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AN UNDESCRIBED TYPE OF ERYTHROPOIESIS OBSERVED IN HUMAN STERNAL MARROW

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Many investigators have believed that megaloblasts and normoblasts follow independent lines of development. Ehrlich [1] maintained that normoblasts are found in normal bone marrow and that megaloblasts are present in embryonic blood and in the blood of patients with relapsing pernicious anemia. He did not observe transitions from one to the other. Pappenheim [2] supported this view, with the exception that he held that under normal conditions megaloblasts can be transformed into normoblasts by gradual proliferative differentiation.

On the other hand, Doan, Cunningham and Sabin [3] and others [4] found cells in normal human marrow which they interpreted to be megaloblasts and precursors of normoblasts. These investigators found no sharp morphologic differences between the early erythroid elements of embryonic life, those of normal adults, those of patients with conditions such as pernicious anemia and those of laboratory animals.

Developmental stages of megaloblasts are observed along with normoblasts in the marrow of patients with pernicious anemia during relapse or early remission. A megaloblastic marrow can be converted by liver therapy almost entirely to normoblastic marrow in twenty-four to forty-eight hours. This rapid disappearance of the megaloblastic cells raises a question as to the mechanism by which it is accomplished.

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The observation of a hitherto undescribed type of erythrogenesis in human sternal marrow is the subject of this report. Amitotic and multipolar erythropoiesis have been observed in aspirated sternal marrow from a man dying of an unusual condition. Along with this type of erythroid development normal bipolar mitosis also occurred. Since the unusual findings in the marrow in this case appear to throw some light on the controversial megaloblast-normoblast problem, they seemed worthy of a detailed report.

REPORT OF A CASE

A white man 77 years of age entered the hospital Dec. 7, 1939 and died Jan. 15, 1940. Two weeks before he entered the hospital, he complained of a sudden sharp pain in the precordium and dizziness. About one hour after this episode a physician who examined him found the temperature 100 F., the pulse rate 102 and the blood pressure 142 systolic and 70 diastolic. The patient was ordered to remain in bed. Electrocardiograms made forty-eight hours and seventy-two hours after the onset of the sudden illness were normal. He did not complain again of pain at any time but spoke of weakness and frequency of urination. Physical examination by the physician mentioned did not reveal any pathologic changes, and rectal examination showed that the prostate was small and firm but smooth. The red blood cell count was 2,450,000 and the leukocyte count 4,300 per cubic millimeter. The sedimentation rate (Wintrobe tube) was 26 mm. per hour. The blood sugar amounted to 115 mg. and the nonprotein nitrogen to 33 mg. per hundred cubic centimeters; the carbon dioxide content of the blood was 72 cc. The patient was then admitted to the hospital. He stated that he had had typhoid fever at the age of 45 and a linear skull fracture in an automobile accident at the age of 64.

Examination in the hospital gavé essentially negative results except that there was frequency of urination, which the patient said had troubled him for the past fifteen years. He complained of pain in the head of the right humerus, but physical as well as roentgen examination showed nothing abnormal. Because of the marked anemia, the patient was given several blood transfusions, various liver extracts and thiamine hydrochloride.

During his entire illness the patient never at any time complained of pain except that accompanying the difficulty in urination. Flat roentgenograms made of the stomach and the liver were normal. On Jan. 11, 1940 the stool showed a 2 plus reaction for blood, but subsequent stools were negative for blood. However, his skin became jaundiced. After three days the jaundice disappeared. The urine at first showed faint traces of albumin and bile and a few granular casts. The bile and casts disappeared within eleven days after the patient's admission to the hospital.

During the remainder of his stay the urine showed only a faint trace of albumin, and the specific gravity varied from 1.020 to 1.024. On December 16 he was unable to urinate (anuria). He was catheterized and 1,100 cc. of dark-colored urine was obtained. The next day he was again catheterized and 900 cc. of urine was obtained. The urine showed many leukocytes, and culture of the catheterized urine was positive for Bacillus pyocyaneus. A Foley retention catheter was then inserted and remained in the urinary bladder until suprapubic cystotomy was performed on Jan. 1, 1940. The second culture of the urine also showed B. pyocyaneus. Repeated blood cultures were negative.

Following the operation, his temperature rose to 105 F. (rectal) and his pulse rate to 125; the respirations were 30 per minute and remained at this level for three days, when orthopnea, marked dyspnea and cardiac fibrillations suddenly developed. The lungs became edematous, and in spite of the use of oxygen and various forms of intravenous therapy, he died three days after the cystotomy and seven weeks and four days after the onset of the illness.

During his stay in the hospital he received four blood transfusions of 500 cc. each and several intramuscular injections of liver extract. He was also given thiamine hydrochloride. Repeated chemical examinations of the blood gave normal results. On admission his temperature was 100 F. and he had a low grade septic temperature ranging from 99 to 102 F. for each hour until the operation, when it suddenly went up to 105 F. His pulse rate fluctuated from 85 to 110 and the respiratory rate from 20 to 30 per minute. During the suprapubic cystotomy the surgeon noticed that the perivascular tissues were friable and markedly injected, and it was with extreme difficulty that he was able to manipulate the tissues.

The urinary bladder showed marked cystitis, and the prostate gland was small and firm but smooth. At the time of surgical intervention there was no clinical evidence of cancer

in the prostate or the urinary bladder. The final clinical diagnosis was acute urinary retention and prostatic obstruction associated with cystitis and pyelitis due to infection with B. pyocyaneus.

Autopsy.—Gross Observations: Both lungs lay free in the pleural cavity. They were pale red to gray and crepitant throughout. On section they were pale red-gray but otherwise were essentially unchanged. The bronchi were slightly dilated and were free of foreign material. The tracheobronchial lymph nodes appeared unchanged.

The pericardial sac was smooth and glistening and contained about 5 cc. of straw-colored fluid. The heart was slightly larger than its owner's fist, pale brown and of the usual cardiac consistency. The mitral valves showed an ancient fibrous thickening on the free edge. The tricuspid valves, the pulmonary artery and valves, and the aorta and valves presented no gross pathologic changes. The coronary vessels appeared uninvolved.

The peritoneum was everywhere smooth and glistening. The spleen was larger than normal, red and somewhat soft. On section the pulp was soft and showed evidence of follicular hyperplasia. The liver was pale yellow-brown. There was no gross evidence of cancer. The gallbladder was unchanged.

Both kidneys were equal in size and of the same shape and consistency. The capsule stripped with slight difficulty, leaving a slightly roughened surface. On section the cortex and the medulla were within normal limits and otherwise appeared unchanged. The adrenal glands showed no pathologic changes except autolysis in the medulla. The pancreas was pale pink-gray and firm and on section presented a gray–pale pink area throughout. The urinary bladder was firmly adherent to the surrounding structures. The mucosa was markedly inflamed, and the prostate gland was smooth. On section there were several areas of abscesses but no gross evidence of cancer in the prostate or the urinary bladder. The gastrointestinal tract revealed no pathologic changes. There was no evidence of cancer in the stomach, and the retroperitoneal lymph nodes were small and appeared unchanged.

Anatomic Diagnosis.—Suppurative cystitis and perivesical abscesses; focal abscesses in the prostate gland.

Microscopic Observations.—Liver: The lobules were separated by small zones of fibrous tissue. The entire section presented a honeycomb appearance due to diffuse degeneration of fat. The central vein was unchanged. The hepatic cords were separated and the spaces filled with a granular material. The hepatic cells showed indistinct outlines; many were swollen, and some had edematous nuclei. The outlines of fat cells were seen not only within but between the hepatic cells. The bile capillaries were essentially unchanged. The capsule of the liver was uninvolved, and there was a small focus of round cells beneath the capsule.

Kidneys: The glomeruli showed in some places a granular deposit in the space beneath Bowman's capsule. There were a few that showed hyaline degeneration. The tubules presented indistinct outlines of the cells in some places, with granular cytoplasm, and the nuclei were absent in some of the cells and somewhat swollen and eccentrically placed in others. The lumens of some of the tubules were filled with pink-staining casts; in others there was a granular deposit, but the majority were free. The blood vessels did not show unusual changes.

Prostate Gland: One of the sections showed an increase of fibrous tissue and some of the glands were dilated: the glands that were not dilated contained concretions. There was no evidence of cancer in the sections. Sections taken from different areas of the prostate gland showed a preponderance of fibrous tissue over the glandular area and except for a focus of inflammatory change, did not show anything remarkable.

Urinary Bladder: Section showed marked invasion by leukocytes, including polymorphonuclears, in the muscular wall as well as in the mucosal portion of the bladder. There was no evidence of cancer.

Spleen: Except for marked hyperemia, the spleen did not reveal any unusual change.

Pancreas: The islands of Langerhans and the acinous structures did not present any unusual pathologic change. Near the periphery of the section there was a slight increase of fat tissue. The blood vessels and the pancreatic duct were uninvolved.

Other Organs: The adrenal glands, the lymph nodes, the heart and the lungs showed no remarkable pathologic changes. The sections of the bone marrow showed no evidence of cancer.

Histologic Diagnosis.—Focal areas of abscesses in the prostate gland; acute suppurative cystitis and perivesiculitis.

Hematologic Studies.—Blood: The essential findings are recorded in table 1. It will be noted that the anemia was normocytic and that the mean diameter of the erythrocytes was normal. The reticulocytes were 4 per cent, and the icteric index was 7.5 units. The sedi-

mentation rate of the red blood cells was 20 mm. per hour (Wintrobe tube), which is twice the normal for man. The number of blood platelets appeared much reduced on examination of a blood smear. The differential count showed: "reticulum and blast cells" 4 per cent; cells of the granulocytic series with grade 3 to 4 "toxic" granulations, 34 per cent; eosinophils, 1 per cent; basophils, 2 per cent; monocytes and monocytoid cells, 25 per cent, and lymphocytes, 33 per cent. There were signs of severe pathologic erythropoietic regeneration, consisting of marked poikilocytosis, basophilic stippling, Jolly bodies, Cabot's ring bodies, karyorrhexis and unusual types of nucleated red blood cells. Moderate anisocytosis and polychromasia were noted, and 5 atypical normoblasts were counted among 100 leukocytes. Daily examinations of the blood over a period of thirty-eight days showed hemoglobin values of 7.6 to 11.3 Gm. per hundred cubic centimeters of blood, erythrocyte counts of 2,510,000 to 3,250,000 per cubic millimeter and leukocyte counts ranging between 2,450 and 13,250

TABLE 1.—*Studies of Peripheral Blood* *

Date of Study	Hemoglobin, Gm.	Erythrocytes, Millions	Leukocytes, Thousands	Mean Corp. Vol., Cubic Microns	Mean Corp. Hemoglobin Concentration, per Cent	Reticulum and "Blast" Cells	Neutrophilic Myelocytes	Neutrophilic Metamyelocytes	Stab Forms	Polymorphonuclear Neutrophils	Lymphocytes	Monocytes and Monocytoid Cells	Eosinophils	Basophils	Normoblasts Among 100 White Blood Cells
12/ 8/39	7.8	2.54	5.25	90.0	33.0	4.0	0.0	3.0	12.0	19.0	33.0	26.0	1.0	2.0	5.0
1/15/40	9.1	3.20	13.25	Color index 0.88	Color index 0.88	36.0	3.0	8.0	7.0	5.0	11.0	26.0	2.0	2.0	35.0

* Only those studies of the peripheral blood made on the first day of the patient's stay in the hospital and those made prior to his death have been selected from a series of thirty-eight hematologic examinations.

TABLE 2.—*Studies of Marrow*

	Erythroid					Myeloid									
Date of Study	Atypical Erythroid Cells	Pronormoblasts	Basophilic Normoblasts	Polychromatophilic Normoblasts	Orthochromatic Normoblasts	Reticulum and "Blast" Cells	Promyelocytes	Neutrophilic Myelocytes	Neutrophilic Metamyelocytes	Band Forms	Polymorphonuclear Neutrophils	Monocytes and Monocytoid Cells	Eosinophils	Basophils	Myeloid-Erythroid Ratio
12/ 8/39	6.0	10.0	42.0	12.0	30.0	12.0	14.0	22.0	36.0	8.0	4.0	0.0	4.0	0.0	0.5 : 9.5
1/15/40	25.0	10.0	4.0	51.0	10.0	90.0	3.0	0.0	0.0	0.0	0.0	5.0	2.0	0.0	0.58: 0.42

per cubic millimeter. Except during the terminal leukocytosis, most of the white cell counts were 5,000 and lower. Studies of the blood one day before the patient's death showed a slight rise in the hemoglobin and in the erythrocyte values (table 2) with a color index of 0.88 per cent, a normal mean cell diameter, leukocytosis and a differential picture made up of "reticulum and blast" cells 36 per cent, monocytes and monocytoid cells 26 per cent, lymphocytes 11 per cent and cells of the granulocytic series 26 per cent. Thirty-five atypical normoblasts were observed in the differential count of 100 leukocytes. The hematologic diagnosis was leukemic reticuloendotheliosis.

Sternal Marrow: [5] Ninety-five per cent of the marrow elements represented normal and pathologic types of erythroid cells. Granulopoiesis and megakaryopoiesis were markedly decreased. Two distinct, unrelated types of erythropoiesis were present; the first was normoblastic with normal bipolar mitosis as the mechanism of cell division, and the second type

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was pathologic with multipolar mitosis, multinucleated erythroid cells and cells with bizarre nuclear configuration a common feature.

The pathologic or bizarre type of erythropoiesis had its origin from the reticulum, after which the cells seemed to lose the ability to divide, but the nuclei did not. Some of the later states of development of these giant cells seemed to be more megaloblastic than normoblastic; however, they were so abnormal that they should be called gigantoblasts[6] rather than true megaloblasts. The earliest stage of the bizarre type of erythropoiesis was a cell that measured 45 by 50 microns in diameter and had a nucleus 35 by 40 microns in diameter. Cells as large as young megakaryocytes and others the size of pronormoblasts had many of the morphologic features of reticulum cells. The chromatin took the form of a coarse stippling

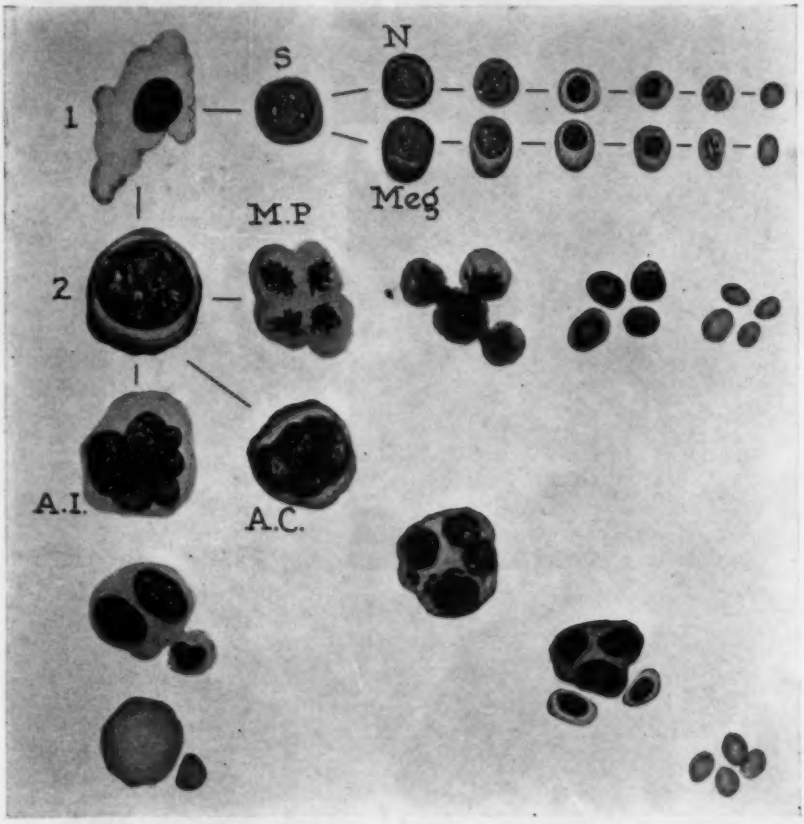

Fig. 1.—Photograph of a water color chart showing the origin and relationship of cells of the hemoglobiniferous series under normal and under pathologic conditions.

1, reticuloendothelial cell. *S* is the stem cell, *N* the normoblastic series of developmental stages and *Meg* the megaloblastic series of developmental stages.

2, giant erythroblast stem cell (gigantoblast) showing the three bizarre types of development. *M.P.* shows the multiple and complicated mitotic divisions of the nucleus and finally the individual or complete separation of the multinucleated erythroblastic cell, each fragment with a portion of the cytoplasm, to form a quantity of erythroblasts. *A.C.* shows erythrogenesis by a process of folding, indentation, lobulation and constriction of the original single nucleus. Finally several independent erythroblast nuclei are produced. In *A.I.*, by a method of complete and incomplete complicated amitosis without cytoplasmic division, a multilobulated erythroblastic cell is formed; fragmentation of the cytoplasm with and without portions of the nucleus and large non-nucleated corpuscle formation are also illustrated.

6. Ehrlich, P., and Lazarus, A.: Anemia, translated by H. W. Armit, New York, Rebman Co., 1909.

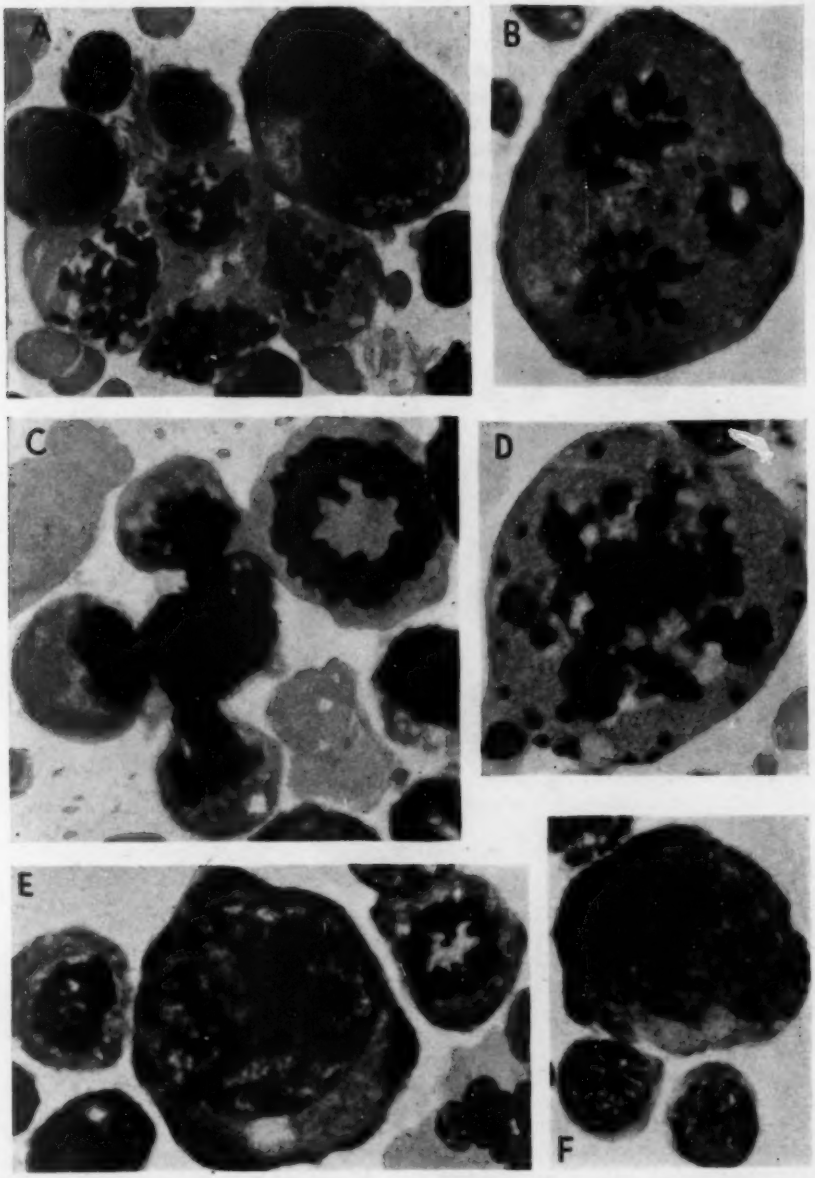

Fig. 2.—*A*, multipolar mitosis showing four groups of chromosomes (quadripolar). Note the gigantoblast in the upper right corner of the field.

B, multipolar mitosis showing three groups of chromosomes (tripolar).

C, formation of four normoblasts from a cell of the quadripolar type of mitosis.

D, mitosis of a gigantoblast with numerous aberrant chromosomal masses in a basophilic cytoplasm.

E, giant erythroblast stem cell (gigantoblast). Note the two erythroid cells in mitosis.

F, giant erythroblast showing folding and indentation of the nucleus.

All the cells in this and the subsequent figures are stained with May-Grünwald-Giemsa stain. The magnification of all cells is × 1,1,00, except *A* and *F* in figure 4 and *E*, *F* and *G* in figure 7. the magnification of which is × 800.

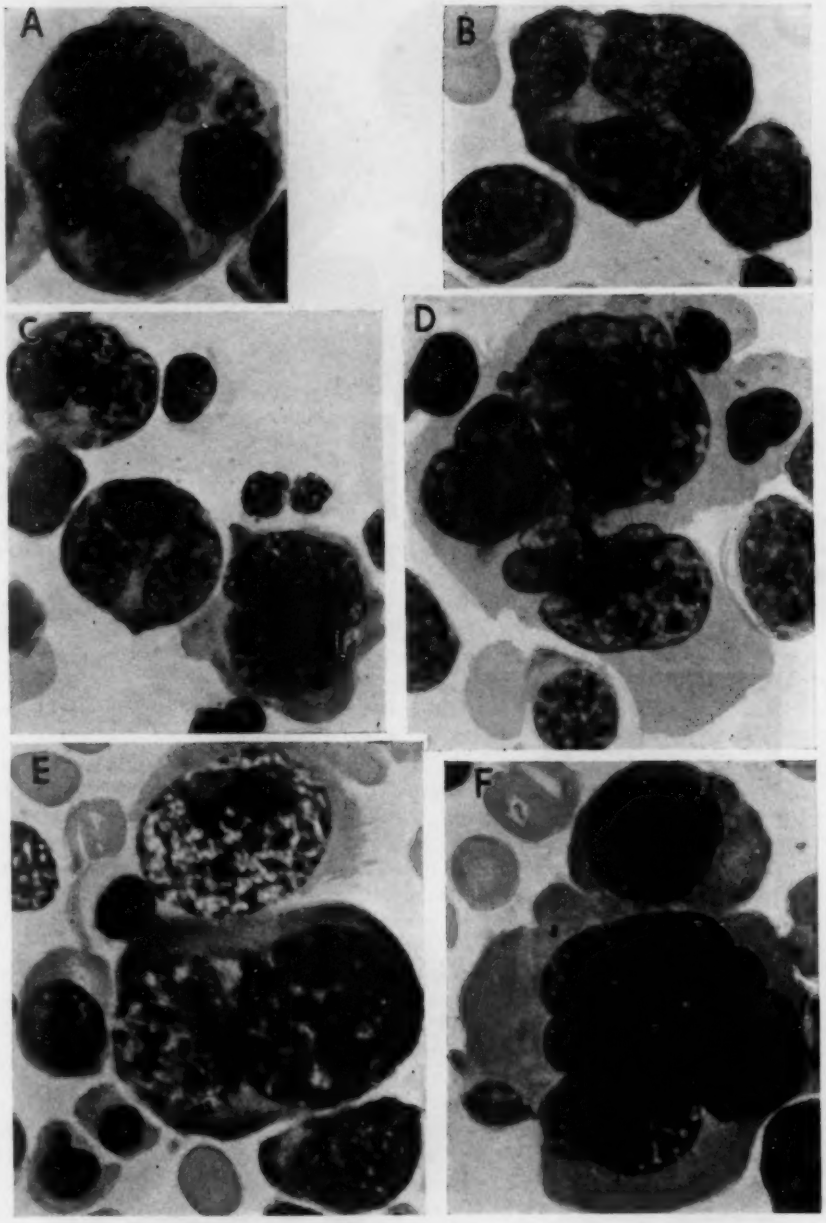

Fig. 3.—*A*, giant erythroblast showing constriction of nucleus.

B, formation of a quantity of erythroblasts from the original single nucleus of the gigantoblast (giant erythroblast).

C, several phases of bizarre erythroid development by a process of indentation, lobulation and constriction of the single nucleus of the giant erythroblast.

D, large complicated tortuous polymorphic nucleus of the cell type seen in *C*. Note the large amount of orthochromatic cytoplasm that surrounds the nucleus.

E, amitosis of a gigantoblast showing disparity and disorganized maturation of the nuclei and cytoplasm.

F, formation of a large complicated tortuous polymorphic nucleus by a process of incomplete complicated amitosis of the single nucleus of the giant erythroblast without cytoplasmic division.

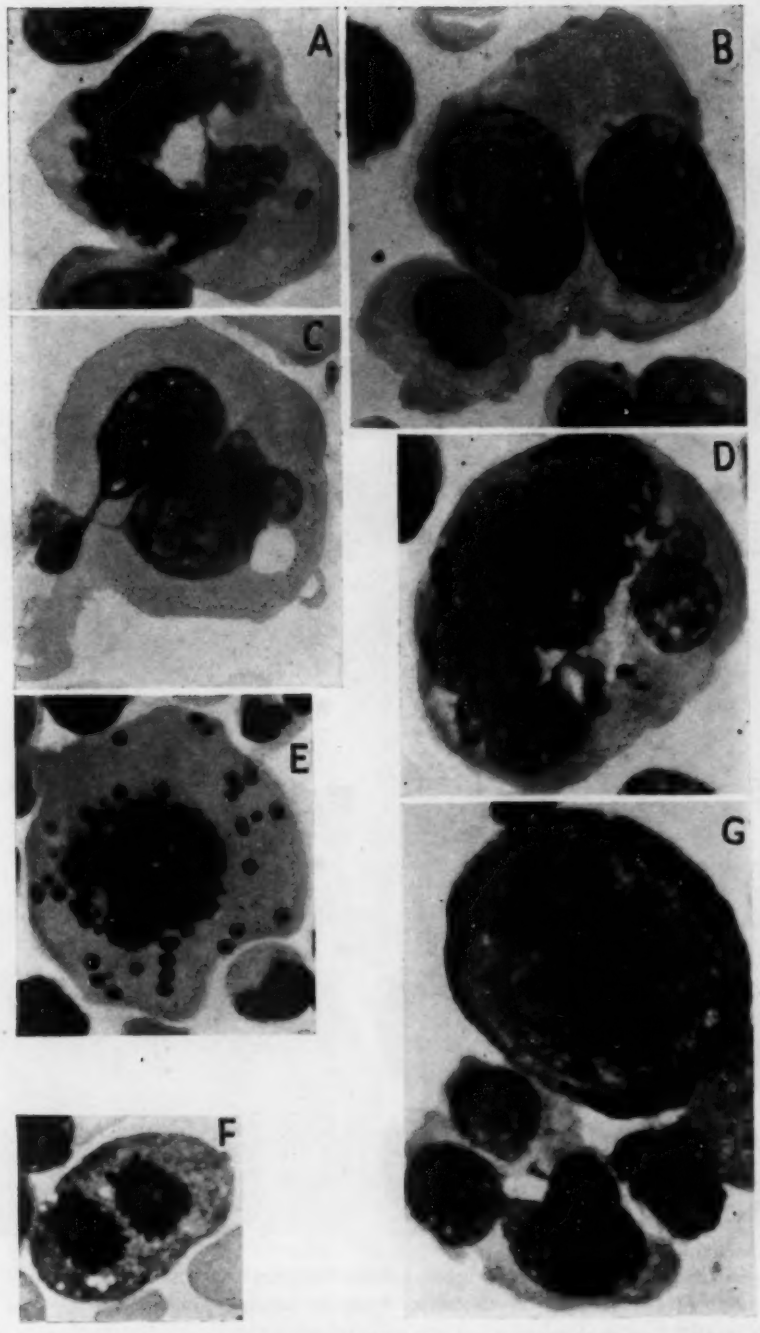

Fig. 4.—*A*, pathologic mitosis of an erythroid cell, showing stickiness, clumping, pyknosis and fusion of the chromosomes during anaphase.

B and *C*, cytoplasmic fragmentation of the orthochromatic gigantoblasts with portions of the nucleus.

D, gigantoblast showing indentation and constriction of the nucleus and formation of buds and bits of nuclear material in the cytoplasm of the cell.

E, loss of the nucleus of a giant erythroblast through karyorrhexis and formation of numerous nuclear particles.

F, normal bipolar mitosis from bone marrow of the same patient.

G, giant erythroblast. Note the formation of a quantity of normoblasts from a cell of the giant erythroblast type.

which was uniformly distributed throughout the nucleus. In a few cells there were small masses of clumped chromatin, so that the chromatin-parachromatin relationship was not distinct. The several nucleoli were indefinite, irregular and pale bluish and often were not sharply separated from the chromatin. The parachromatin was slightly acidophilic. The homogeneous cytoplasm was deeply basophilic, with a small definitely acidophilic area simulating a globule situated near the nucleus. The giant erythroblast cells proceeded along one of the following bizarre lines of development: (1) by a series of multiple and complicated mitotic divisions of the nucleus without cytoplasmic separation a multinucleated cell was formed. Multipolar mitosis was seen in basophilic, polychromatophilic and completely hemoglobinized (acidophilic) cells. Individual or complete separation of the multinucleated erythroblastic cells with a portion of the cytoplasm took place, forming a quantity of erythroblasts which matured to erythrocytes; (2) by a process of folding, indentation, lobulation and constriction of the original single nucleus several independent erythroblast nuclei were produced. Basophilic, polychromatophilic and orthochromatic (acidophilic) stages of this multiple intracellular erythroblastic method of erythrogenesis were observed. At any one of the several stages of development, whether basophilic, polychromatophilic or acidophilic, the multinucleated cell might suddenly form separate or independent groups of erythroblasts, which then proceeded to become mature erythrocytes; (3) by a method of complete and incomplete complicated amitosis without cytoplasmic division, multinucleated normoblastic cells or large complicated tortuous polymorphic nuclei were formed. Some of the latter cells were seen in the process of cytoplasmic fragmentation with or without portions of the nucleus; others formed non-nucleated corpuscles as large as 23 by 27 microns in diameter by extrusion of the large complicated multilobulated nuclei. Fragmentation of the large red cells occurred in the marrow, since they were never observed in the peripheral blood.

Disparity and disorganized maturation between the nucleus and the cytoplasm were the predominant feature of this pathologic erythrogenesis. Karyorrhexis with many bizarre nuclear protuberances, nuclear buds and bits, and swollen and misshapen nuclei, karyolysis and pathologic structural denucleation were seen during the various stages of red cell development in the marrow and to a less extent in the peripheral blood.

Whether one or several mechanisms were responsible for the unusual pathologic erythropoiesis could not be determined accurately. Irregularity in bipolar and multipolar mitoses, such as lagging behind of some chromosomes, which gave rise to aberrant chromatin masses, resulted in extranuclear chromosomes in the cytoplasm. The chromosomes were much shorter and thicker than normal. Stickiness, clumping, pyknosis and fusion of the chromosomes during anaphase brought about an apparent modification of the number and aberrations involving chromatin bridges, deletions and free fragments. Degenerative mitoses occurred in cells in the acidophilic stage which were approaching pyknosis. Multiple nuclear buds—that is, the loss of a nucleus through karyorrhexis—sometimes resulted in a multilobulated structure. The fragmentation might be so excessive as to fill the cell with many nuclear particles. In general the cells which were undergoing rapid and disorganized proliferation passed beyond the stage in which pyknosis and denucleation normally take place, and this resulted in abnormal chromosomes.[7] Granulocytes and their precursors were few. Early forms of the granulocytic and monocytic series presented complex and bizarre nuclear configurations, such as large bands, holes, peculiar protuberances and invaginations. These cells were also seen in the peripheral blood.

The examination of the sternal marrow approximately one hour after death showed some changes due to autolysis. There were numerous extremely immature cells, which looked as if they might have come from the reticulum. They were not typical of free reticular cells, and they were not identical with myeloblasts. The bizarre type of erythropoiesis was present, but only the later stages were evident. One must consider the postmortem changes in judging these cells. Multipolar mitosis was absent. The extremely immature or undifferentiated cell was much larger than the monocyte of reticular origin seen in the peripheral blood in cases of subacute bacterial endocarditis. The nucleus was eccentrically placed and consisted of chromatin strands that were rather straight and coarse, with angular interspaces. The nucleoli were irregular in outline, faintly bluish and pale, and not sharply separated from the chromatin strands. Some cells had a nuclear pattern that was fine and more leptochromatic, with sharply outlined nucleoli that definitely stained bluish. There was no attempt at chromatic condensation to indicate the possibility of differentiation. The cells were irregular in shape

and contained a number of azure granules and rods in a slightly basophilic cytoplasm. Others were free of any granules and had a dark basophilic border of cytoplasm. Monocytoid cells with lobulated, sharply indented or grooved nuclei were present. The few megakaryocytes observed appeared normal. Cells of the granulocytic series showed toxic nuclear and cytoplasmic changes.

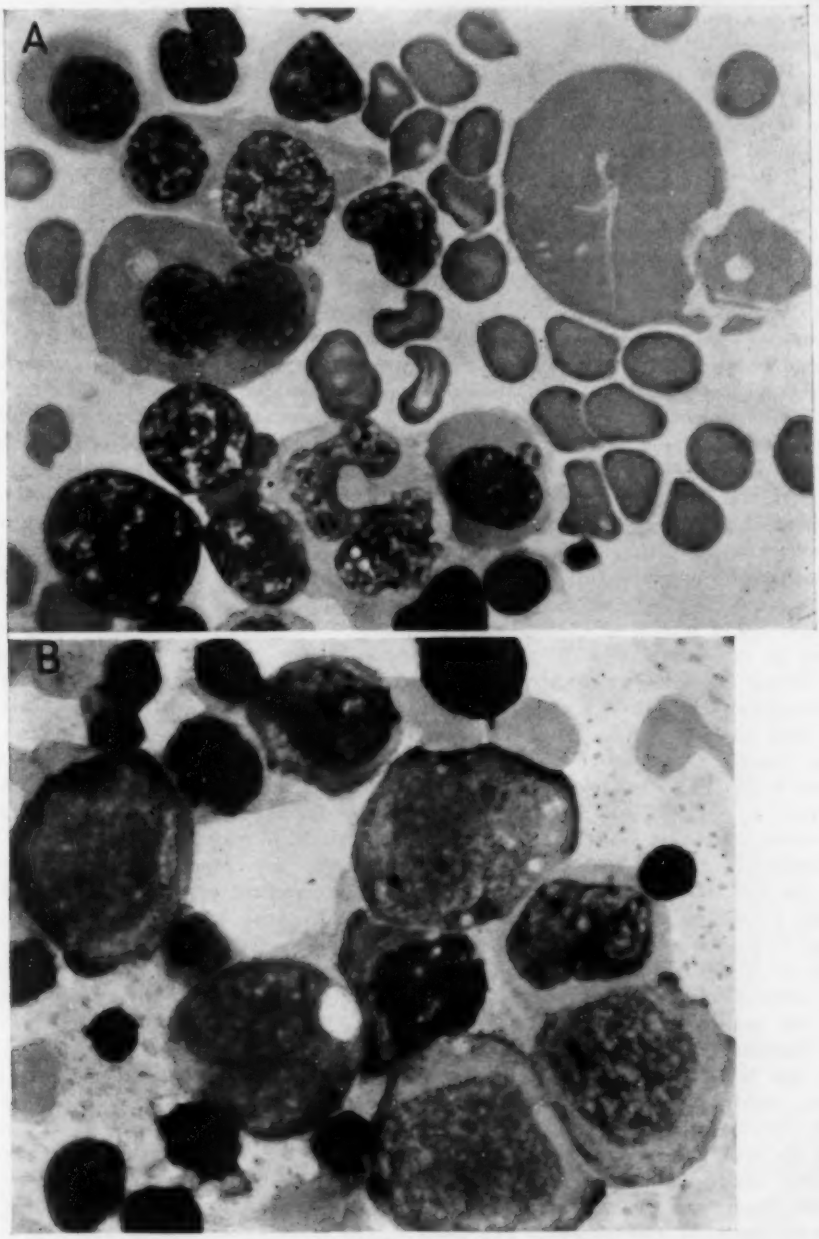

Fig. 5.—*A*, bizarre erythrogenesis. Note the large non-nucleated corpuscle (23 microns by 27 microns in diameter) showing beginning fragmentation of the cell. *B*, marrow pattern taken at the time of the death of the patient, showing extremely immature or undifferentiated cells and a few normoblasts.

COMMENT

Fieschi,[7] Michels,[8] Maximow,[9] Rohr,[10] Jones,[11] Fallon,[12] Wilson,[13] Moeschlin [14] and Bloom and Bartelmez [15b] have published excellent reviews on the subject of embryonic, normal and pathologic erythropoiesis; therefore only those references pertinent to the present case will be mentioned.

Normal erythropoiesis is homoplastic in type. The circulating red cells are continually being formed from immature and early types of normoblasts in the marrow. Transitional forms between the stem cell and the erythroid cell in the marrow are rare. In embryonic life and in pathologic conditions in the adult organism heteroplastic erythropoiesis, the development of red blood cells by proliferation and differentiation of the stem cell in the marrow, is observed.

The "stem cell" and the earliest stage of red cell production are known by various names, each depending on the particular or modified school of hematology favored by the investigator. The "stem cell" has been called undifferentiated mesenchymal cell, reticulum cell, endothelial cell, histiocyte, hemohistiocyte, hemohistoblast, primitive "blast," lymphocyte, lymphoidocyte, hemocytoblast, micromyeloblast and myeloblast; the first stage of the hemoglobiniferous series has been referred to as primary erythroblast, secondary erythroblast, erythroblast, proerythroblast, pronormoblast, megaloblast, hemoblast, lymphoid cell, erythrogone and erythrogonium. Both the "stem cell" and the first stage of the hemoglobiniferous series have been given as the origin of the erythrocyte in embryonic life and under pathologic conditions in the normal adult. In general all investigators agree that the non-nucleated erythrocyte is formed from a stem cell by a process of differentiation, bipolar mitosis and maturation.

The opinions of Ehrlich [1] and Pappenheim [2] in contrast with those of Doan, Cunningham and Sabin [3a] and others [4] have been mentioned. Ferrata,[16] Naegeli [17] and Jones [11] emphasized the distinguishing features of both normoblasts and megaloblasts in relation to their nuclear pattern and cytoplasmic changes. Bloom and Bartelmez [15b] in discussing hemopoiesis in young human embryos divide the

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16. Ferrata, A.: Le emopatie, Milan, Società editrice Libraria, 1933-1935.

17. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931; Wien. klin. Wchnschr. **48**:225, 1935.

formative red blood cells into the primitive and the definitive generation, arising from similar stem cells and developing through roughly parallel but morphologically distinct series of erythroblasts. The relation of these two forms of erythropoiesis in pernicious anemia has been given by Jones [11a] in a comprehensive review.

Both pronormoblasts and megaloblasts can be developed from the reticulum in the adult under certain pathologic conditions and, as Downey [18] has stated, it probably requires very unusual conditions to bring on this type of erythropoietic development. Ferrata [16] derived megaloblasts from "hemohistoblasts." It is claimed that these cells are damaged parenchymal cells [19] and not true reticuloendothelial elements. The myeloblastic origin of megaloblasts has many supporters,[20] while a few investigators [21] introduce an erythrogonial phase between the stem cell and the megaloblast stage. Endothelium [17] and mesenchymal tissue [22] have been given as the origin of megaloblasts. Fontana [23] expressed belief in both a hemohistoblast and a hemocytoblast derivation of the megaloblast. Our case supports the opinion that erythroid elements have their origin from very immature, undifferentiated cells, i. e., reticulum and mesenchyme.

The multinucleated erythroblast cells in our case are not to be confused with polykaryocytes formed by nuclear fusion,[24] osteoblasts, phagocytic histiocytes, multinucleated plasma cells or *Normoblastensyncytium* or ascribed to stickiness or clumping of erythroblasts or normoblasts. They are not similar to tumor cells seen in metastatic lesions of the marrow. Except for their megakaryocytoid character, with a large complicated and tortuous multilobulated nucleus, they have no relation either morphologically or hemopoietically to true platelet-forming magakaryocytes in the marrow. Morphologically, they are different from the true megaloblasts of pernicious anemia and from the pronormoblasts seen in normal marrow and in the marrow of patients with hemolytic anemia due to extrinsic or intrinsic factors.[5] They are different from multinucleated erythroblasts seen in embryonic blood during the prehepatic period.[25] The unusual erythroid cells have not been observed in normal or pathologic conditions following administration of such toxic agents as sulfanilamide,[26] colchicine [27] and arsenic.[28] Downey,[29] Jones [30] and Isaacs [31] have never seen such an unusual type of erythropoiesis. We have studied over 2,325 sternal biopsies [32] and not once observed this type of erythroid development.

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18. Downey, H.:. The Myeloblast: Its Occurrence Under Normal and Pathological Conditions and Its Relations to Lymphocytes and Other Blood Cells, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1965.
19. Ringoen, A. R.: Folia haemat. **33**:149, 1927.
20. (*a*) Tempka, T., and Braun, B.: Folia haemat. **48**:355, 1932. (*b*) Nordenson, N. G.: Studies on Bone Marrow from Sternal Puncture, Stockholm, Börtzells Esselte, 1935; (*c*) Hematopoiesis from Sternal Puncture, Acta med. Scandinav. (supp.) **78**:185, 1936. (*d*) Segerdahl, E.: Ueber Sternalpunktionen, Uppsala, Appelberg, 1935. (*e*) Weiner, W., and Kaznelson, P.: Folia haemat. **32**:233, 1926. (*f*) Jones.[11a]
21. Henning, N.: Deutsche med. Wchnschr. **61**:1543, 1935. Jaffe, R. H.: Folia haemat. **49**:51, 1933.
22. Barta, I.: Deutsches Arch. f. klin. Med. **171**:565, 1931.
23. Fontana, L.: Arch. per le sc. med. **52**:497, 1928.
24. Jordon, H. E.: Am. J. Anat. **19**:277, 1916; **24**:225, 1918; **26**:1, 1919.
25. Jones, O. P.: Personal communication to the authors.
26. Paul, J. T., and Limarzi, L. R.: Proc. Soc. Exper. Biol. & Med. **43**:29, 1940.
27. Paul, J. T.; Brown, W. O., and Limarzi, L. R.: Am. J. Clin. Path. **11**:210, 1941.
28. Limarzi, L. R.: Proc. Central Soc. Clin. Research **15**:12, 1942.
29. Downey, Hal.: Personal communication to the authors.
30. Jones, O. P.: Personal communication to the authors.
31. Isaacs, R.: Personal communication to the authors.
32. Limarzi, L. R.: Proc. Inst. Med. Chicago **14**:144, 1942.

The predominant cells seen in the blood and the marrow prior to the patient's death appeared to have their origin in the reticulum. Although most of the cells were undifferentiated, a few showed partial differentiation to atypical monocytoid cells as indicated by the finding of a lobulated, sharply indented or grooved nucleus with fine azure dust or azure granules and rods in the cytoplasm. Some cells had a very basophilic cytoplasm.

It is of interest to note that in spite of the presence of many large erythroblasts and multinucleated elements in the marrow the anemia was normocytic-normochromic in type. This indicates that the predominant type of erythropoiesis is normoblastic in character and results in formation of a large number of normal size erythrocytes or that large non-nucleated cells never reached the blood stream. Some multinucleated giant erythroblasts form non-nucleated corpuscles as large as 23 by 27 microns in diameter, which is followed by fragmentation of the cell since they were not observed in the peripheral blood.

That the reticulum in the marrow is involved in erythropoiesis is obvious from a study of the material. The pathologic cells are not genuine megaloblasts, nor are they macronormoblasts. None of the organs showed any indication of leukemia [32a] or extramedullary hemopoiesis. The giant erythroblasts are suggestive of something cancerous. The best impression at the present time is a cancerous process of the reticulum differentiating along hemoglobiniferous lines, i. e., *erythroma* or *erythroblastoma*. Apparently, in unusual conditions calling for rapid formation of red cells the reticulum can revert to unusual types of erythrogenesis. In this case the reticulum undergoes an irreversible change comparable to a cancerous or a leukemic process.

The occurrence of normal bipolar and pathologic multipolar mitosis of erythroid cells in the same marrow is an unusual finding in the adult. Maximow,[9] Knoll and Bloom pictured erythropoiesis of the multipolar type in human embryos. Bloom described it in embryos of the rat, the cat and the mouse; Storti, in chick embryos and Kirschbaum and Jones in embryos of the rat.[33] Stilwell [34] was able to evoke multipolar mitosis in normal embryonic chick connective tissue cells grown in vitro. The cells were given no experimental treatment other than exposure to visible light for a period of twenty minutes previous to fixation. Multinucleated erythroblast development involving multipolar mitosis as a rapid and normal type of erythropoiesis in the early human embryo is an interesting speculation which awaits further investigation. Multipolar mitosis has been seen in the marrow in pernicious anemia in relapse.[35] The observations in our case together with those in human and animal embryos support the belief that the erythropoiesis in pernicious anemia shows a pathologic development rather than a purely functional disturbance conditioned by demand.

The exact nature of what occurs to the marrow in pernicious anemia during the first twenty-four to forty-eight hours after the intramuscular administration

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32a. Several investigators have described cases in which, while the blood picture seemed to justify the diagnosis of leukemic reticuloendotheliosis, the organs showed no spectacular evidence for the origin of the leukemic cells from the reticulum (Monocytic Leukemia and Leukemic Reticulo-Endotheliosis, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 1275). As Downey has stated, the reticulum is apparently used up in the production of atypical leukemic cells.

33. Jones, O. P.: Personal communication to the authors. Dr. Jones was kind enough to send one of the authors (L. R. L.) a dry smear from the yolk sac of a rat embryo illustrating multinucleated erythroblasts.

34. Stilwell, E. F.: Anat. Rec. **76**:205, 1940.

35. Limarzi, L. R.; Jones, R. M., and Levinson, S. A.: Anat. Rec. **19**:43, 1941. Rohr.[10] Fieschi.[7] Limarzi, L. R.; Levinson, S. A., and Jones, R. M.: J. A. M. A. **118**:1004, 1942.

of liver extract is a much discussed question. It has been demonstrated that the megaloblastic marrow of a patient with pernicious anemia in relapse is eventually transformed into normal-appearing marrow.[36] The unsettled question regards the mechanism underlying this dramatic conversion or transformation which occurs so rapidly after specific antianemic therapy. Many investigators[37] have maintained that megaloblasts complete their maturation as megalocytes and do not mature into cells of the normoblastic series. According to Jones,[111] the latter cells reappear and return to normal function by heteroplastic development from the reticulum and/or the myeloblasts and by homoplastic development from the quiescent remnants of the normoblastic series present in the marrow during relapse. There are those who find megaloblasts in normal marrow and believe that the megaloblastic marrow in pernicious anemia is due to a lack of a hemopoietic principle which is needed for the maturation of megaloblasts to normoblasts.[38] Wilson [13] expressed the belief that the cells of the definite normoblastic series can develop from the megaloblastic series or from the pronormoblasts. Davidson, Davis and Innes [39] supported the thesis that megaloblasts and normoblasts belong to one developmental series and that the former develop into the latter under the influence of liver therapy. Segerdahl [40] and Rohr [10] expressed the opinion that amitotic division must be responsible for the rapid erythropoietic change that occurs in the marrow in pernicious anemia during a relapse. Segerdahl reported that in marrow obtained from a patient with pernicious anemia twenty-four hours after an injection of liver extract few mitotic figures were seen in proportion to the tremendous normoblastic proliferation, which must be largely the result of amitotic division. Koller [36b] expressed the opinion that young multinucleated megaloblastic cells may subdivide and heteroplastically form a quantity of normoblasts.

Multipolar mitosis and multinucleated giant megaloblasts are not uncommon in the marrow in cases of pernicious anemia in relapse.[35] In normal marrow only bipolar mitosis is observed and even in cases of severe erythroid immaturity this is the only type of cell division noted. One of us (L. R. L.) [41] has shown that the megaloblast of pernicious anemia is arsenic sensitive and that the pronormoblast seen in normal marrow and in the marrow of most patients with anemia showing erythroid immaturity is arsenic resistant. Further that the liver principle can exert its rapid physiologic effect on the marrow in pernicious anemia in the presence of a karyorrhetic megaloblastic tissue which presumably is in a poorly functional condition due to the toxic effect of arsenic. This is additional evidence for the separation of the pathologic megaloblastic series from the normoblastic series of red cell regeneration. Jones [42] in a comprehensive

36. (*a*) Scott, R. B.: Quart. J. Med. **8**:127, 1939. (*b*) Koller, F.: Deutsches Arch. f. klin. Med. **184**:568, 1939. (*c*) Wiener and Kaznelson.[20e] (*d*) Peabody.[4d] (*e*) Nordenson.[20b] (*f*) Rohr.[10]

37. Mustafa, K.: Ztschr. f. klin. Med. **136**:416, 1939. Storti, E.: Haematologica **18**:1, 1937. Tischendorf, W.: Deutsches Arch. f. klin. Med. **187**:556, 1941. Fieschi.[7] Naegeli.[17] Rohr.[10] Segerdahl.[20d] Jones.[11]

38. Henning, N.: Deutsche med. Wchnschr. **39**:1543, 1935. Lambin, P., and de Weirdt, W.: Rev. belge sc. méd. **10**:282, 1938. Schulten, H.: Die Sternalpunktion als diagnostische Methode, Leipzig, Georg Thieme, 1937. Schartum-Hansen, H.: Folia haemat. **58**:145, 1937. Doan.[3b] Isaacs.[4a] Osgood and Haskins.[4b] Koller.[36b] Peabody.[4d] Sabin and Miller.[4f]

39. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Quart. J. Med. **11**:19, 1942.

40. Segerdahl, E.: Acta med. Scandinav., 1935, supp. 64, p. 1.

41. Limarzi, L. R.: J. A. M. A. **121**:1245, 1943.

42. Jones, O. P.: Arch. Path. **35**:752, 1943.

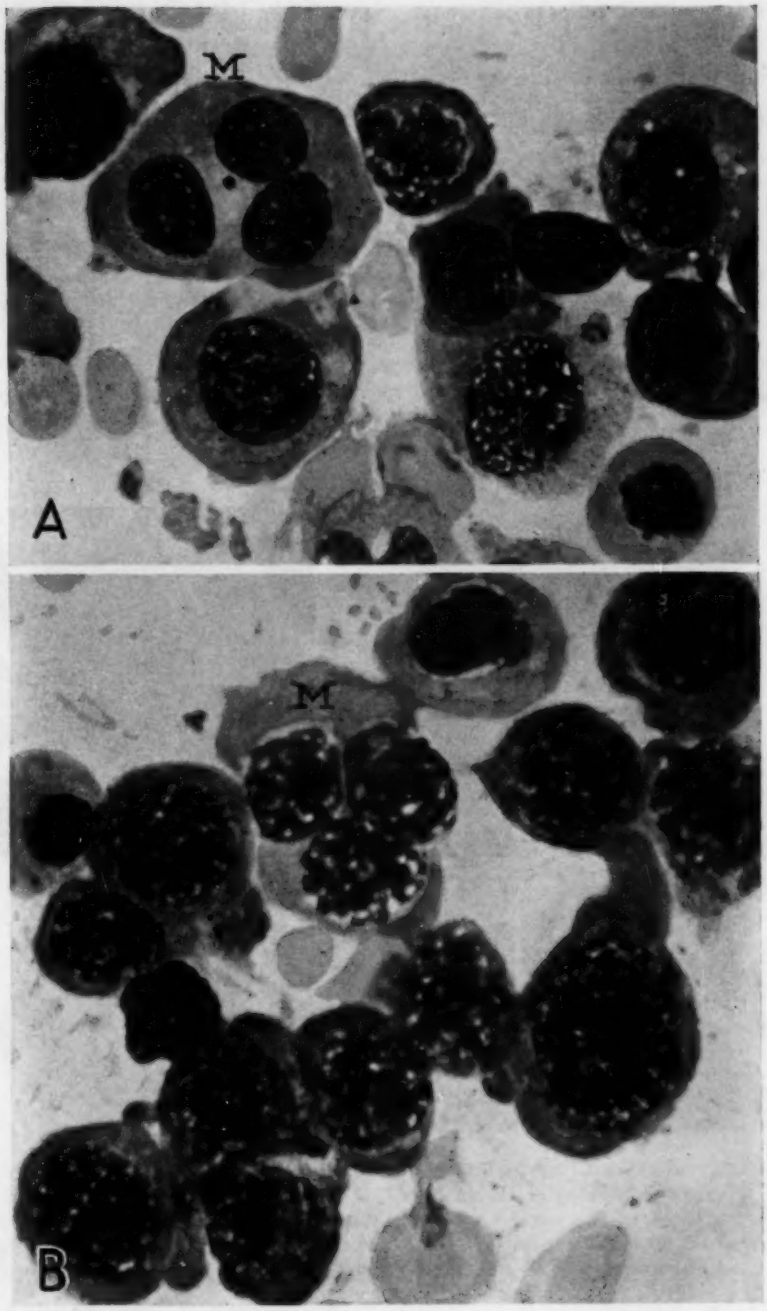

Fig 6.—*A*, marrow from a patient with pernicious anemia in relapse, showing megaloblasts and a multinucleated erythroblast (*M*). *B*, marrow from same patient as *A*, taken forty-eight hours after an intramuscular injection of 10 cc. of liver extract (20 units); it illustrates the tremendous normoblastic conversion or transformation. Note the multinucleated normoblast cell (*M*).

review on morphologic, physiologic, chemical and biologic distinction of megaloblasts has detailed evidence for the separation of the megaloblastic and normoblastic series of red cell development. In a study of 2,325 sternal marrows one of us (L. R. L.) has observed megaloblasts almost entirely, if not exclusively, in patients with anemia due to deficiency of liver principle. Rohr [10] has had a similar experience in a series of more than 1,800 biopsies of marrow.

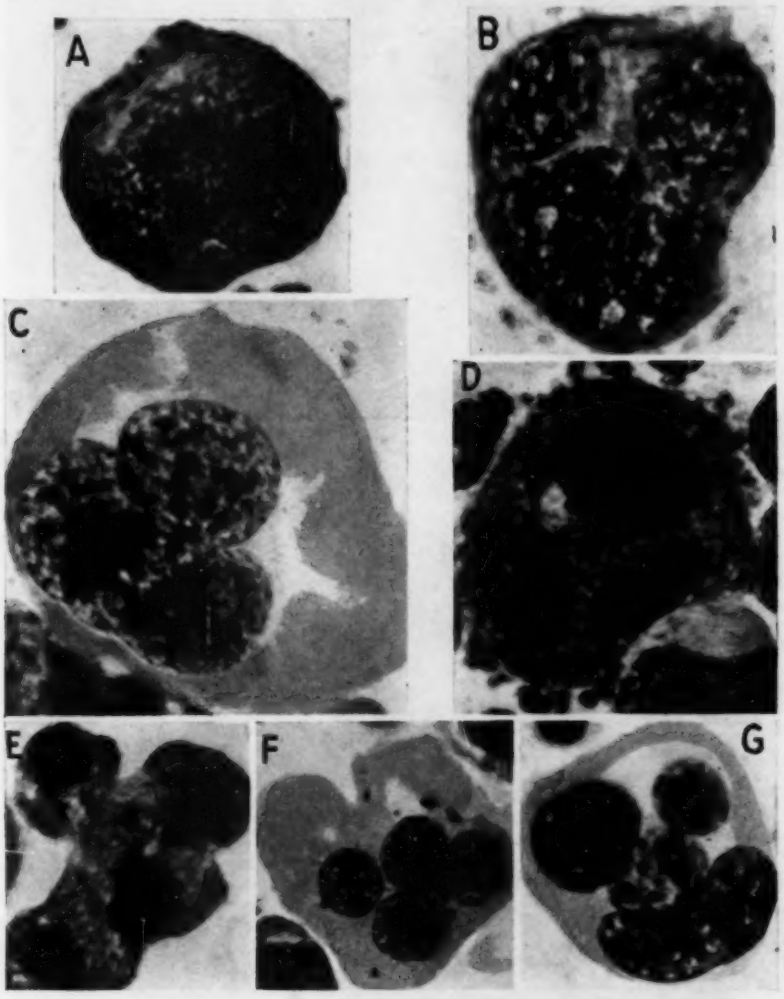

Fig. 7.—*A*, megaloblast. *B*, multinucleated erythroblast. *C*, multinucleated megaloblast. *D* and *E*, multiple mitosis in erythroid cells. *F*, multinucleated erythroid cell. *G*, indentation and constriction of the nucleus of an erythroid cell, showing the method of formation of a quantity of normoblast nuclei. *D* to *G* were taken twenty-four to forty-eight hours after intramuscular injection of 10 cc. of liver extract (20 units). All the cells shown in figure 7 are from the bone marrow of patients with pernicious anemia.

We have studied the marrow in some 200 cases of pernicious anemia in various stages of relapse and remission and have observed marrow with a preponderance of megaloblasts in various stages of megaloblastic maturation converted into marrow almost entirely normoblastic twenty-four to forty-eight hours after intramus-

cular injection of large doses of liver extract. Naegeli[17] has reported that megaloblasts disappear from the marrow eight days after therapy and has expressed the belief that it is incorrect to assume that they have matured to normal red cells.

It is our contention that the mechanism underlying the dramatic conversion or transformation of megaloblastic marrow to normoblastic marrow in less than forty-eight hours after institution of liver therapy is in part due to the involvement of multipolar mitosis and large multinucleated erythroid cells in pernicious anemia. It must be emphasized that single-nucleated megaloblasts cannot transform into normoblasts but that multinucleated ones can. There are several facts which lend support to this thesis: (1) Arsenic-sensitive pathologic megaloblasts do not mature to normoblasts; (2) the small number of normoblasts present in the marrow in pernicious anemia in relapse are insufficient in themselves to produce such a tremendous proliferation of normoblasts in so short a period as forty-eight hours, since normally it requires about five days for pronormoblasts to mature to normoblasts,[10] and (3) the mechanism by which multipolar mitosis and multinucleated erythroblasts produce a quantity of normoblasts is suggested by the unusual type of erythropoiesis reported in this paper.

SUMMARY

For the first time a type of erythropoiesis is reported in which giant erythroblasts, by an unusual and pathologic mechanism, form normal and pathologic erythroid cells. The condition is suggestive of erythroblastoma.

The mechanism of the rapid conversion of the megaloblastic marrow in pernicious anemia to normoblastic marrow after liver therapy is explained in part by the involvement of multipolar mitosis and multinucleated erythroblasts in the production of a quantity of normoblasts.

The contention that there are independent types of erythropoiesis with cells developing along separate lines in the marrow in pernicious anemia in relapse is supported by the experiments and observations reported in this paper.

CARCINOMA WHICH SIMULATES SARCOMA

A STUDY OF 110 SPECIMENS FROM VARIOUS SITES

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MANCHESTER, N. H.

Any large series of cancers will include a certain small proportion of obviously highly malignant ones which cannot be classified as to their possible epithelial or mesenchymal origin. Only too frequently the final diagnosis of these must be cancer, grade 4. This study has been made of tumors from various organs which were diagnosed as carcinoma but which differed from carcinoma as ordinarily found in these organs in such a manner that they were or might have been mistaken for sarcoma. The histologic features of these tumors have been studied in order to determine how they may be classified definitely as of epithelial origin rather than as of mesenchymal or indefinite origin.

LITERATURE

Extreme anaplasia is an important factor in the production of the atypical growths which are the subject of this paper. Hansemann [1] related the development of anaplasia to asymmetric mitosis among the tumor cells. More recently Lewis and Strong [2] have indicated that in spontaneous tumors of mice difference in degrees of malignancy as shown by rates of growth and periods of survival was probably on a genetic basis.

Kettle,[3] Broders [4] and Ewing [5] have noted the sarcoma-like appearance of some human neoplasms classed as carcinoma. So-called carcinosarcoma is related to the subject of this paper. Theories of its origin were presented by Virchow [6] and Krompecher.[7] Harvey and Hamilton [8]

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* When this work was done Dr. Brooks was a Fellow in Pathology at the Mayo Foundation.

1. Hansemann, D.: Virchows Arch. f. path. Anat. **119**:299, 1890.

2. Lewis, M. R., and Strong, L. C.: Am. J. Cancer **20**:72, 1934.

3. Kettle, E. H.: The Pathology of Tumors, New York, Paul B. Hoeber, Inc., 1916, pp. 49 and 116; Proc. Roy. Soc. Med. (Sect. Path.) **12** (pt. 3):1, 1919.

4. Broders, A. C.: Ann. Surg. **73**:141, 1921.

5. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 268, 292, 785, 852, 921, 990 and 1050.

6. Virchow, R.: Die krankhaften Geschwülste, Berlin, August Hirschwald, 1864-1865, vol. 2, p. 182.

7. Krompecher, E.: Beitr. z. path. Anat. u. z. allg. Path. **37**:28, 1905; **44**: 88, 1908.

8. Harvey, W. F., and Hamilton, T. D.: Edinburgh M. J. **42**:337, 1935.

and Saphir and Vass [9] have expressed the belief that certain human tumors of this type must be considered true carcinoma, the sarcomatous appearance of some of the carcinoma cells being due to anaplasia, infection, previous application of roentgen radiation or mechanical pressure.

Roussy, Leroux and Wolff [10] stated that they had never seen carcinoma turn into sarcoma or vice versa. They had noted certain tar cancers of mice composed of fusiform cells resembling sarcomatous fibroblasts. They expressed the belief that these were true epithelial tumors, giving the following reasons: (1) Tar cancers which are clearly squamous frequently have such areas of fusiform cells, between which and the clearly carcinomatous areas are all stages of transitional cells; (2) sometimes pearly bodies (islands of keratinizing epithelium) can be seen in the midst of fusocellular areas; (3) sometimes lesions metastatic from tumors which seem to be composed entirely of fusiform cells show unmistakable squamous cell characteristics.

Martin and Stewart [11] have presented a clinical and pathologic study of 8 cases of spindle cell carcinoma of the skin. They emphasized the role of previous scarring or of irradiation of the tissue as a possible factor in the development of the morphologic peculiarity in question. The results following treatment were unsatisfactory. They noted transitions between the basal layers of the epidermis and the sarcoma-like tumor tissue.

Carcinoma arising from other areas than the skin has been noted to resemble various forms of sarcoma. The so-called lymphoepithelioma can be confused with the reticulum cell or the small cell types of lymphosarcoma. The origin of such cancer from epithelium has been recognized,[12] and it has been considered to be a variety of anaplastic squamous or transitional cell carcinoma.

In the lung, what used to be known as mediastinal or oat cell sarcoma has now generally come to be recognized as carcinoma.[13] Among tumors of the thyroid gland, adenocarcinoma resembling sarcoma has been described.[14] Among tumors of the genitourinary tract, carcinoma of the

9. Saphir, O., and Vass, A.: Am. J. Cancer **33**:331, 1938.

10. Roussy, G.; Leroux, R., and Wolff, M.: Le cancer, in Roger, G. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine, ed. 2, Paris, Masson & Cie, 1929, vol. 5, pt. 2, pp. 526 and 563.

11. Martin, H. E., and Stewart, F. W.: Am. J. Cancer **24**:273, 1935.

12. Ewing, J.: Am. J. Path. **5**:99, 1929. Harvey, W. F.; Dawson, E. K., and Innes, J. R. M.: Edinburgh M. J. **44**:549, 1937. New, G. B., and Kirch, W.: Arch. Otolaryng. **8**:600, 1928. Schmincke, A.: Beitr. z. path. Anat. u. z. allg. Path. **68**:161, 1921.

13. Barnard, W. G.: J. Path. & Bact. **29**:241, 1926. Weller, C. V.: Arch. Path. **7**:478, 1929.

14. Broders, A. C.: West. J. Surg. **48**:620, 1940. Smith, L. W.: Arch. Path. **10**:524, 1930. Ewing.[5]

bladder imitating sarcoma has been reported,[15] and possible confusion between carcinoma and lymphosarcoma of the prostate gland has been noted.[16]

MATERIAL AND METHODS

Sections from approximately 850 tumors were examined in order to select cases for study. In addition to cases of carcinoma of a high degree of malignancy, instances of sarcoma of various types and of various degrees of malignancy involving tissues in which carcinoma is more common were included. From this number, 144 were selected for further study on the basis of a sarcomatous appearance, whether the original diagnosis was carcinoma or sarcoma. An attempt was made to prove a carcinomatous origin by finding an area in which the transition from obvious carcinoma to sarcoma-like cells was good or by finding an area in which the sarcoma-like structures were differentiated toward recognizable epithelial structures such as epithelial pearls or glandular acini. Besides finding such proof of epithelial origin, an estimate was made of the amount of infection and necrosis present, the number and the distribution of mitotic figures and the incidence of asymmetric mitosis, the number of tumor giant cells, the degree of fibrosis and vascularity and the incidence of invasion of blood vessels by the tumor.

Clinical data were obtained on the duration of the tumor, the presence of previous disease in the region, the nature of previous treatment, the treatment given at the Mayo Clinic and the outcome as far as it was recorded.

Tissues were not recut if the sections at hand showed sufficient proof of epithelial origin, unless a special stain was desirable. Most of those which were recut or from which new blocks were taken were those in which an epithelial origin seemed possible but in which the original sections revealed no differentiated or transitional area.

Most of the tissues, including all of the surgical material and the gross specimens removed at necropsy from which new blocks were cut, were fixed in approximately 4 per cent solution of formaldehyde. The original blocks of tissue obtained at postmortem examination were fixed in Orth's solution. All sections, whether cut from a paraffin block or after freezing, were stained with hematoxylin and eosin. Other stains used were (1) a modification of the Mallory-Heidenhain stain for tissues fixed in solution of formaldehyde, (2) the Van Gieson stain for connective tissue,[17] (3) the Perdrau[17] and Gömöri[18] stains for reticulum and (4) de Galantha's[19] stain for mucin.

In addition to the 144 sarcoma-like tumors which formed the basis of this report, numerous tumors known to represent fibrosarcoma and lymphosarcoma were studied. These served as controls for the use of the special stains and as sources of information concerning histologic details.

Because of the highly selected character of the collection of tumors ultimately proved to be carcinoma, detailed statistical analysis would be unreliable. Of the

15. McDonald, J. R.; Doss, A. K., and Thompson, G. J.: J. Urol. **46**:38, 1941.

16. Cappell, D. F.: Glasgow M. J. **124**:177, 1935. Cole, F. H., and Martin, L. R.: J. Urol. **31**:803, 1934. Randall, A., and Hughes, B.: Tr. Am. A. Genito-Urin. Surgeons **22**:245, 1929. Ewing.[5]

17. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938.

18. Gömöri, G.: Am. J. Path. **13**:993, 1937.

19. de Galantha, E.: Am. J. Clin. Path. **6**:196, 1936.

144 tumors selected for study, 110 proved to be carcinoma. Tumors were included from eight different organ systems or regions of the body as follows: skin and lip; mouth; nasopharynx; larynx; lung; gastrointestinal tract; genitourinary tract and thyroid gland. Many neoplasms of the breast and the uterus were examined, but no good example of a cancer proved to be carcinoma strongly resembling sarcoma was found.

SKIN, LIP AND MOUTH

Carcinoma arising from the epithelium of the skin or the lip formed the largest group among the cancers collected, and this group was the most intensively studied. There were several reasons for this. Similar lesions had been less studied by others than lesions similar to the tumors of the other groups. The exposed position of the tumors of the skin and the lip made it easy to obtain them and to evaluate the history of past disease in the regions involved, and of previous treatment. More of them represented early or small lesions since they had been more noticeable to the patients. Hence, points of origin and transitional areas were found more easily. In several instances a section of the entire tumor could be mounted.

For inclusion of a lesion in this group, the usual criterion was that it should be a diffuse cancerous growth of spindle-shaped cells. Not all the cancers included were entirely composed of cells of this type. A good many cancers composed entirely of spindle-shaped cells but with an alveolar arrangement were found but not included.

Melanoma frequently is composed entirely of spindle-shaped cells and could well be confused with carcinoma of the type under consideration. No tumors about which there was a question of a possibly melanomatous character were included in this study.

Among the 110 cases of cancer proved to be carcinoma the only group subjected to any statistical analysis was that of 28 selected cases of carcinoma of the skin and the lip, composed of fusiform cells. In all these instances the malignancy was grade 4. In 23 (82 per cent) some previous treatment for carcinoma or some other disease had been given to the involved region prior to registration at the clinic. In 14 (61 per cent) a caustic or diathermy had been used locally. In 13 (57 per cent) roentgen rays or radium had been applied.

It has been pointed out by others that the presence of scar tissue might be associated with the assumption of a spindle shape by the tumor cells, but many of these tumors showed almost no intercellular collagen and little peripheral collagen. In others the tumor cells were individually buried in masses of collagen. Whether this represented stroma as in scirrhous carcinoma or was preexisting invaded fibrous tissue could not be determined; previous trauma as given in the history, however, could not be correlated with the presence of spindle cells. The use of the Van Gieson and the Mallory-Heidenhain connective tissue stain did not help clear up this point.

The amount of infection was extremely variable, although in the majority of cases it was minimal or there was no infection. The average number of abnormal and of normal mitotic figures varied extremely not only among different tumors but in different parts of the same tumor. The number ranged from 1 per 15 high power fields (× 400) to 4 per single high power field. Tumor giant cells generally were infrequent or absent. Invasion of blood vessels was seen twice.

Regional nodes were dissected in 4 cases. In only 1 was a metastatic tumor found. In this case the metastatic cells resembled those of the primary tumor and were entirely spindle shaped. In 3 other cases regional nodes were involved grossly, but no tissue except that from the primary lesions had been removed.

Among the 28 patients there were 7, or 25 per cent, who were found to have lived five years or more after operation. In those known to be living the average diameter of the lesion at the time of registration was 1.4 cm. In those known to be dead the average diameter of the lesion at the time of registration was 2.8 cm.

In studying the transitional tissue between sarcoma-like tissue and the surface epithelium, particular attention was given to the presence of asymmetric mitotic figures in the basal layers of the surface epithelium and to disintegration of the basement membrane. To be considered asymmetric a mitotic figure had to be Y shaped or X shaped or to have a definite inequality between two well separated masses of chromatin. Although asymmetric mitosis may occur in other situations than malignant tumors,[20] its presence in the malpighian layer of the epidermis was considered corroborative evidence for the presence of an epithelial cancerous process, and usually it was associated with other findings indicative of such a process, such as enlarged and hyperchromic nuclei, enlarged nucleoli and loss of intercellular bridges. Had asymmetric mitosis been seen in such a situation without other evidence of connection between the epithelium and the underlying cancer, it would have been disregarded. It was not seen in epithelium overlying fibrosarcoma or lymphosarcoma, even though that epithelium sometimes showed many large hyperchromic nuclei and normal mitotic figures.

Although in the tumors with sarcomatous appearance the fusiform cells usually seemed to arise in the basal layers of the epidermis, in 1 instance (case 6) there were islands of fusiform carcinoma cells in the upper layers of the epidermis. This seems to indicate, more than anything else, that the factor which determines the assumption of the spindle shape is not extrinsic or due to some change in the tissues invaded by the tumor but is more likely due to a property intrinsic in the tumor cell.

20. Wassermann, F.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1929, vol. 1, pt. 2, p. 347.

Tumors of this nature from the mouth and the tongue presented no features greatly different from those of the skin and the lip. The average amount of infection was greater, however.

CASE 1.—A woman aged 49 years complained of a firm warty nodule of a few weeks' duration just superior to the left nasal ala and measuring 1.5 cm. in diameter. For sixteen years she had had eczematous scaling and blanching on her nose, for which she had had many roentgen treatments. The nodule was removed with cautery, and radium was applied.

Histologically, the tumor was composed of a diffuse mass of intertwining fusiform cells. Surface epidermis was not present. On the borders of the sections was considerable necrosis, and under this were large numbers of lymphocytes. The tumor cells mixed with the lymphocytes tended to be rounded or polygonal. The deeper layers were free of infection, and here the tumor was composed of fusiform cells. In the midst of these cells were a few small areas of typical squamous carcinoma cells with a slight amount of keratinization. Mitosis was infrequent, and about a third of the mitotic figures seen appeared abnormal.

Nine months after removal of the tumor there was a recurrence at the same site. This was treated successfully. The patient was reported living without any recurrence six years and four months after the original operation.

CASE 2.—A man 38 years of age had had roentgen treatments for facial acne fourteen to sixteen years before admission. Twenty months before, a cancer had been removed from his nose. Two months before, a large red hard mass had developed on the columella. This was removed with diathermy.

Histologically, a mass of fusiform tumor cells was connected with the surface epithelium by several good transitional areas (fig. 1 *a*). In the basal layers of the epidermis were many cells with large hyperchromic nuclei and numerous mitotic figures, some of which were abnormal. The deeper fusiform tumor cells were embedded in dense collagen, which made up an estimated 50 per cent of the tumor mass. Here mitotic figures were numerous (averaging 2 per high power field), and a small percentage of them were asymmetric. The nuclei of the tumor cells were oval or elongated, with a scanty amount of cytoplasm, which appeared compressed between the collagen fibers.

Four months after dismissal from the clinic, the patient wrote that another nodule had appeared in the same location. Whether this was scar or tumor tissue was not determined.

CASE 3.—A man aged 38 years had had a tumor of the lower lip for two and a half months, which had been treated with local chemical cautery several times. The lesion was 1.5 cm. in diameter, and some ulceration was present. Excision was done; the submaxillary and submental regions were given a course of radium, and then the submaxillary nodes were dissected. These did not contain microscopic evidence of metastasis.

In the sections of the tumor studied there was almost no ulceration of the surface epithelium. Transition was evident between the basal cells of the epidermis and the tumor cells, which were fusiform or rounded but closely packed in interlacing bundles with no alveolar arrangement whatsoever. The tumor spread for a considerable distance laterally from its point of origin under normal epidermis. There were numerous lymphocytes around the periphery, but in the main body of the tumor there was no inflammatory reaction except near the point of ulceration. Mitotic figures were not numerous (1 per 3 or 4 high power fields), and no abnormal ones were seen. There were a few giant nuclei. No keratinization was present.

This patient reported that he was well without evidence of recurrence ten years and eight months after operation.

CASE 4.—A man 64 years of age had had numerous keratoses of the face and neck. About six months before registration he noted a smooth, slightly red but

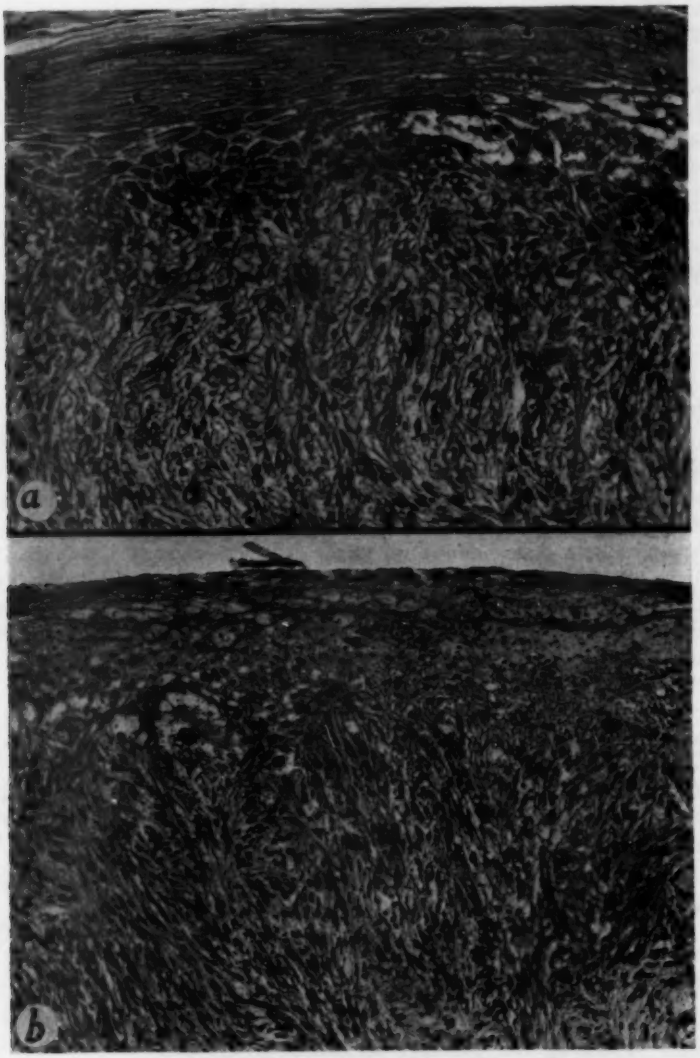

Fig. 1.—Transition from surface epithelium to sarcoma-like tumor cells; a large amount of collagen can be seen: (*a*) Tissue from the nose in case 2 (hematoxylin and eosin; × 135); roentgen or radium therapy had previously been applied in this region. (*b*) Tissue from the neck in case 4 (hematoxylin and eosin; × 105); no previous roentgen or radium therapy had been given.

nonpigmented firm nodule, .6 mm. in diameter, in the skin of the neck. The tumor was composed of irregularly arranged masses of fusiform cancerous cells

with considerable interspersed collagen. Transition between the basal layers of the intact epidermis and the fusiform tumor cells was well marked (fig. 1 *b*). Many of the cells in the deeper layers of the epidermis had large hyperchromic nuclei, and there were many mitotic figures in these layers. No definitely asymmetric mitotic figures were identified. A Gömöri reticulum stain of the transitional area showed an absence of the basement membrane at this point, while laterally the epidermis covering the tumor mass had a well developed, conspicuous basement membrane. This stain also showed a well developed intercellular reticulum and considerable collagen in the tumor. There was no alveolar arrangement. Invasion of blood vessels and epithelial pearls were not noted. Tumor giant cells were numerous.

Reports from this patient indicated no recurrence at the site of the tumor one year and seven months after operation.

CASE 5.—A woman aged 50 years had had a raised reddish indurated lesion, measuring 1 cm. in diameter, with a central crust, on the right ankle for one year. This was widely excised.

Microscopic examination of sections of the tumor revealed considerable keratinization of the surface epithelium but no ulceration. Under the thickest portion of keratin the epidermis, though intact, was thinned, and the cells of the basal layer were disorganized and had enlarged hyperchromic nuclei. One asymmetric mitotic figure was seen in this layer. Immediately under the epidermis there was rapid transition to smaller fusiform tumor cells, which were arranged irregularly. Deeper there were large interlacing bundles of the fusiform cells. The tumor extended laterally under normal epidermis. Its borders were indefinite; the tumor cells in the corium became fewer and fewer as the distance from the point of origin increased. Mitotic figures were infrequent (1 per 10 high power fields). No tumor giant cells were seen. Gömöri stains for reticulum revealed no evidence of basement membrane at the point of origin of the tumor from the epidermis. Much reticulum and collagen were scattered throughout the tumor. No follow-up report was available on this patient.

CASE 6.—A man aged 66 years had had an ulcer of the arch of the left foot for three years. This was initiated by wearing a rough arch support. It had been treated by home remedies and electrodesiccation. At the time of admission to the clinic the ulcer was 2.5 cm. in diameter and was considered arteriosclerotic or syphilitic. The ulcer was excised, and treatment with radium was given.

The typical alveolar arrangement of squamous cell carcinoma was seen on microscopic examination, but each group of tumor cells was made up of long, narrow fusiform cells. Collagen stains did not demonstrate intercellular collagen in these groups. There was some intraepithelial origin of the tumor cells, where also there were fusiform cells and no collagen. Some of the deeper layers of the tumor, still retaining an alveolar arrangement, were made up of round and polygonal tumor cells. In these areas mitotic figures were slightly more numerous (1 per high power field) than among the sarcoma-like cells (1 per 5 high power fields). Atypical mitosis was rare.

When this patient returned eight months later, he had metastatic lesions of the inguinal and femoral nodes.

NASOPHARYNX AND LARYNX

The nasopharyngeal tumors presented more difficulties in this study than those of any other group. This was due principally to the small amount of tissue available for study and to the invariable presence of

ulceration and infection. The appearance of an area which made one suspicious that it was transitional was difficult to interpret. In the study of this type of tumor a reticulum stain to bring out the basement membrane if present was most useful. It was also an aid in the study of the intercellular reticulum of the tumor. Although in a few cases carcinoma composed mainly of fusiform cells was found, the main difficulty arose in confusion not with fibrosarcoma but with lymphosarcoma.

Carcinoma of the larynx presented no histologic features essentially different from those of carcinoma of the skin. It is of interest to note that in 2 cases (7 and 8) the lesion was considered to be possibly sarcomatous from its gross polypoid appearance.

Case 7.—A man aged 61 years had had hoarseness for two years and aphonia for a shorter period. Tracheotomy had been done elsewhere. At the Mayo Clinic a polypoid tumor, measuring 4 by 2 by 1 cm., attached to the right vocal cord and infiltrating the commissure, was removed by laryngectomy. It presented two types of tissue. On the surface and in scattered clumps was obvious squamous cell carcinoma. Throughout the intervening spaces the tissue closely resembled highly malignant fibrosarcoma. The cells were pleomorphic, mostly fusiform, and giant tumor cells were numerous. No inflammatory reaction was present. Mitotic figures were moderately numerous (1 per 4 high power fields), and about 10 per cent were asymmetric. Several areas showed good transitions between the squamous cells and the fibrosarcoma-like cells. Thus this tumor was a highly malignant squamous carcinoma. This patient was living seven years and three months after operation.

Case 8.—A man aged 66 years had had hoarseness for six weeks. A nodule measuring 7 mm. in length was found attached to the middle and anterior thirds of the right vocal cord. The latter was not fixed. The tumor was removed after thyrotomy. The results of microscopic examination were similar to those in case 7. More infection was present, especially in the way of surface ulceration. A good transition from squamous cell carcinoma to fibrosarcoma-like tumor cells was present. The latter formed most of the tumor mass. Mitotic figures were infrequent, and no asymmetric ones were seen. Mallory-Heidenhain stains showed much intercellular collagen in the sarcoma-like areas and a loss of the basement membrane at the transitional areas. This patient was living without recurrence ten months after operation.

LUNGS

The most striking feature noted in the study of carcinoma of the lungs was the ability of the sarcoma-like cells, whether of the small rounded or of the fusiform type, to differentiate into the squamous and the glandular acinus–forming type in the same tumor (cases 9 and 10). This seems to indicate that the terms "squamous cell carcinoma" and "adenocarcinoma" should be used cautiously when applied to carcinoma of the lungs.

Case 9.—A man aged 51 years had had a productive cough, dyspnea and weakness for seven weeks. Examination pointed to a lesion of the lower lobe of the right lung, and a specimen removed from the right main bronchus during the course of bronchoscopic examination revealed squamous carcinoma, grade 3.

The patient died six weeks after registration. Post mortem, the right main bronchus and its branches were found thickened and stenosed, and the lower lobe of the right lung was diffusely infiltrated by tumor tissue.

Microscopically, this tumor was composed principally of small, irregularly shaped cells, loosely packed together, which had for the most part rounded or elongated oval nuclei. These varied considerably in density of chromatin, but most of them were not as dark as the nuclei of lymphocytes. Mitotic figures and tumor giant cells were infrequent (less than 1 per 10 high power fields). Considerable necrosis and acute infection were present. The pulmonary veins were invaded, and there was generalized metastasis. Most of the metastatic lesions were similar to the principal part of the tumor and could be mistaken for lymphosarcoma. However, a few sections of lung showed numerous areas in which squamous cells were differentiated in the midst of small tumor cells. Another area showed excellent formation of acini by the same small tumor cells.

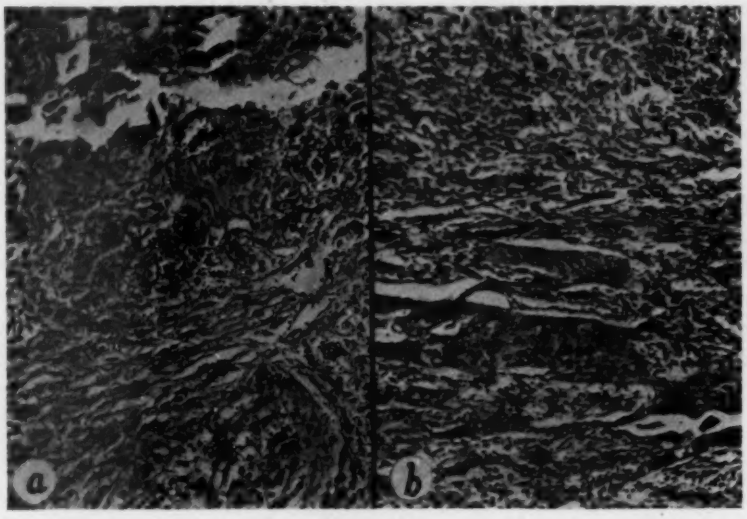

Fig. 2 (case 10).—(*a*) Tissue obtained through a bronchoscope; acini formed by a tumor composed chiefly of fusiform cells in diffuse arrangement (hematoxylin and eosin; × 95). (*b*) Squamous cell differentiation in the same pulmonary tumor as *a* (hematoxylin and eosin; × 65).

This tumor, therefore, was considered to be an anaplastic carcinoma with differentiation in two directions.

Case 10.—A woman aged 52 years had had progressive fatigue, cough and hemoptysis for one year. Examination revealed a rounded, nonpulsating tumor in the left upper anterior portion of the thorax. A transpleural exploration disclosed an inoperable lesion, which at biopsy proved to be a highly malignant cancer composed of a diffuse, closely packed mass of fusiform cells. The size and the density of the nuclei and the arrangement of the cells were irregular. The resemblance to fibrosarcoma was marked. However, at one edge of the section were a few tumor cells forming acini (fig. 2 *a*). This patient died eight weeks after the operation.

Post mortem the upper portion of the left lung was found completely occupied by a tumor which extended into the wall of the chest. Sections of this showed the same diffuse fibrosarcoma-like picture as the biopsy and also a few areas with attempts at formation of acini. Furthermore, there were areas of differentiation into squamous cells similar to those in case 9 (fig. 2*b*). This tumor also was considered to be highly anaplastic carcinoma.

GASTROINTESTINAL TRACT

The cancers of the gastrointestinal tract which resembled sarcoma were chiefly in the stomach. Many esophageal lesions diagnosed squamous carcinoma, grade 4, were investigated, but the structure was always alveolar, although fusiform tumor cells sometimes occurred. Highly malignant cancers of the large intestine and rectum diagnosed as adenocarcinoma suggested lymphosarcoma. Tumors of the anus diagnosed as squamous carcinoma showed fusiform tumor cells in parts.

Nine cancers of the stomach (7 which had been called lymphosarcoma and 2 which had been called fibrosarcoma) were studied. In 4 of those regarded as lymphosarcoma a suggestion of acinus formation was shown in the hematoxylin and eosin preparations, and in 2 of these intracellular mucus was present. One of the cancers considered to be fibrosarcoma was shown to be carcinoma by staining for mucin and by sectioning more blocks, which revealed well formed acini. These cases illustrate how easily the common diffuse small cell carcinoma of the stomach may be mistaken for sarcoma. The presence of signet ring cells with mucus and acini somewhere in the tumor should be sought carefully.

GENITOURINARY TRACT

Carcinoma of the genitourinary tract simulated fibrosarcoma, lymphosarcoma, leiomyosarcoma and myxosarcoma. That of the pelvis of the kidney and the bladder frequently showed papillary or alveolar structures but was also diffusely invasive. In the single case of carcinoma of the urinary bladder in which postmortem examination was performed, all the metastatic lesions were found to be sarcoma-like without any differentiation at all. In a case of carcinoma of the prostate gland which resembled lymphosarcoma, the diagnosis depended on the finding of a differentiated area in a metastatic process.

CASE 11.—A man aged 66 years had had painless hematuria for one month. A tumor was found in the right kidney, and nephrectomy and ureterectomy were performed. The kidney weighed 255 Gm., and a tumor measuring 7.5 by 4.5 by 5 cm. involved the pelvis and extended into the renal substance.

Microscopically, the main mass of the tumor was composed of closely packed parallel fusiform cells. The nuclei were oval and pale and contained prominent large nucleoli. The cytoplasm was scanty. The resemblance to fibrosarcoma was striking. Sections of the renal pelvis revealed a small area in the pelvic epithelium of obvious squamous carcinoma with well marked alveolar construc-

tion. The tissues underlying the pelvis were invaded. No papillary structure was seen. Transition with loss of the basement membrane between squamous carcinoma and the fibrosarcoma-like areas was fairly evident. Near this area were small islands of tumor cells differentiated from the fusiform cells and resembling squamous cells. Keratinization and tumor giant cells were not found. This tumor was considered to be highly malignant squamous carcinoma.

The patient died five months after operation from recurrence in the wound and probable metastasis.

THYROID GLAND

Sarcoma-like carcinoma of the thyroid gland resembled fibrosarcoma. It was difficult to prove an origin from the glandular epithelium by the presence of transitions between the two. It was found that the best evidence could be discovered in metastatic lesions which were well differ-

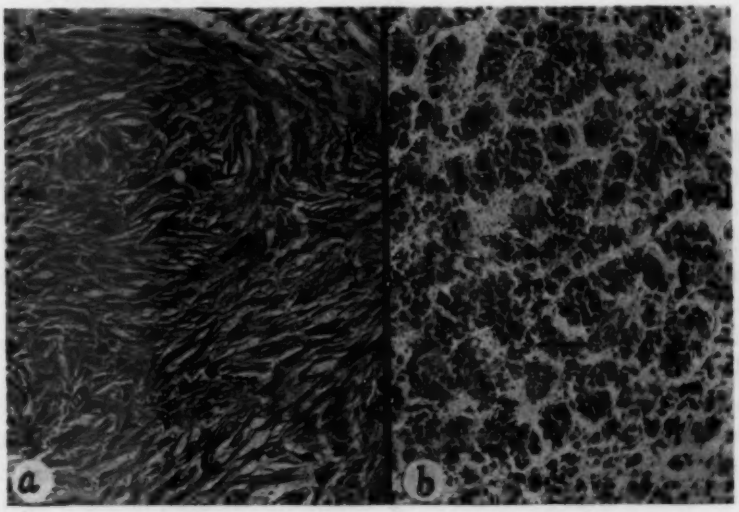

Fig. 3 (case 12).—(*a*) Tissue from a primary tumor in the thyroid gland; it does not give evidence of being a carcinoma (hematoxylin and eosin; × 195). (*b*) Tissue from a metastatic lesion in the brain from the tumor of the thyroid gland shown in *a*; this is unmistakably carcinoma (hematoxylin and eosin; × 120).

entiated (case 12). Infection and necrosis were prominent in the majority of cases. Tumor giant cells were not numerous, although some of the tumors which did not closely resemble fibrosarcoma were pleomorphic. A tumor of the thyroid gland composed of a diffuse growth of small rounded cells was not encountered. In the case which most nearly approached this type the metastatic lesion in one adrenal gland was made up of fusiform cells.

Case 12.—A man aged 57 years had had a goiter for two years with neuralgic pain of the head and neck. Examination revealed a stony hard, almost fixed thyroid gland. Biopsy was done, and roentgen therapy given.

Microscopic examination revealed a diffuse arrangement of fibrosarcoma-like tumor cells with many giant nuclei and 1 to 2 mitotic figures in each high power field, some of which were asymmetric.

The patient died five months later. Post mortem the thyroid gland was seen to be replaced by a diffuse growth of hard white tumor tissue but still having the general shape and size of a small goiter. The trachea and the sheath of the right carotid artery were invaded, and metastatic lesions were present in the brain, adrenal glands, lungs, kidneys and right twelfth rib.

Microscopic examination of the thyroid gland demonstrated essentially the same picture as the biopsy, with no differentiation to indicate an epithelial origin in any of several sections (fig. 3*a*). However, the metastatic lesions of the rib and the brain both showed differentiation toward epithelial characteristics with definite formation of acini. The lesion in the brain (fig. 3*b*) appeared somewhat more anaplastic than that in the rib. The tumor was considered to be carcinoma primary in the thyroid gland.

COMMENT

Attempts have been made previously to distinguish carcinoma from sarcoma by use of special staining methods. White [21] concluded that the amount of elastic tissue in a tumor is determined by that normally present in the tissue in which the growth has arisen. Sarcoma showed increased intercellular connective tissue, while in carcinoma such tissue outlined the cell groups but did not occur intercellularly.

Tureen and Seelig [22] found the amount of reticulum present in carcinoma as shown by a silver impregnation method to be dependent on the kind of tissue in which the tumor was growing but not on the grade of malignancy.

In the present study, collagen and reticulum were stained by the Van Gieson, Mallory-Heidenhain, Perdrau and Gömöri methods. These stains proved useful in very few cases, and chiefly to indicate the presence or the absence of a basement membrane. No significant differences in the amount or the arrangement of the reticulum or collagen between sarcoma and sarcoma-like carcinoma were noted. The reticulum stains were of slight help in distinguishing lymphoepithelioma from lymphosarcoma. The Van Gieson stain furnished no information not shown by the other stains. The stain for mucus was used extensively but was of help only in gastric carcinoma, in which it was decisive.

The factors determining the assumption of a microscopically diffuse sarcomatous appearance by carcinoma cells did not become evident during the study. Most authors have stated that this change is probably due to the characteristics of the invaded tissue, at least as far as the spindle shape is concerned. Scar tissue owing to trauma, irradiation, infection, pressure, or the fasciculated arrangement of the invaded tissue, as in muscle, has been suggested. Several of the most striking examples of

21. White, W. C.: Bull. Johns Hopkins Hosp. **11**:209, 1900.
22. Tureen, L. L., and Seelig, M. G.: Arch. Path. **15**:498, 1933.

carcinoma composed of fusiform cells in this study showed almost no collagen with the Mallory-Heidenhain stain, and many of them showed little or no infection. Previous trauma and irradiation were possibly slightly more frequent in the cases of sarcoma-like carcinoma of the skin and the lip than in cases of typical carcinoma of these tissues. The presence of intraepithelial fusiform cells with malignancy of grade 4 in 1 cancer showed that the influence of the invaded tissue is not necessary. It is felt that probably the fusiform shape is due to an intrinsic characteristic of the tumor cell itself.

SUMMARY

The pleomorphism of cancerous epithelial cells is such that carcinoma may simulate various types of sarcoma. The literature applicable to such morphologic changes in general and to such changes in tumors of particular organs is briefly reviewed.

The microscopic features of 110 tumors that had been proved to be carcinoma simulating sarcoma were studied. Tumors from the skin, lip, oral cavity, nasopharynx, larynx, lung, gastrointestinal tract, genitourinary tract and thyroid gland were presented. They were all of a high grade of malignancy.

The presence of definite transitional areas between recognizable epithelium and sarcoma-like areas and the presence of areas in which the tumor cells had differentiated into recognizable epithelial structures have been discussed and illustrated in relation to diagnosis.

The use of special stains was of definite help only in staining for reticulum in tumors of the nasopharynx and for mucus in tumors of the stomach and in indicating the presence or the absence of a basement membrane in certain cases.

The assumption of a fusiform or rounded shape and microscopically diffuse sarcoma-like growth by carcinoma cells is probably not due to factors in the invaded tissue but is an inherent characteristic of the cells of the particular carcinoma.

CONJUNCTIVAL EXANTHEM IN SPOTTED TYPHUS

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Diagnosing spotted typhus fever in a cadaver offers many difficulties, particularly when the characteristic eruption is mild or has disappeared. Other gross signs of typhus have little diagnostic significance because they are not characteristic and are to be seen in other infectious diseases. At the same time, a pathologic diagnosis of typhus may have an important epidemiologic significance. As far back as 1933, while studying changes in the central nervous system accompanying typhus, in cadavers, I noticed the presence in the conjunctivas of red points and spots. This sign, little noted in the literature and practically unknown to the majority of physicians, is in reality most valuable. During the first three months in 1943 it was found in 94 per cent of the cases of typhus investigated at the Moscow Clinical Institute for Infectious Diseases. In 95 per cent of these cases the cutaneous eruption was indistinct; in 12 per cent it was absent. Thus, the conjunctival spots remained the sole distinguishing sign on gross inspection. The majority of the cases were considered by the clinicians as cases of typhus of medium or grave intensity. The duration of the disease was from eight to seventeen days. The intensity of the spots was about the same in both sexes. They were more numerous and more distinct in young subjects and in subjects of middle age.

In 6 per cent of undoubted cases of typhus gross inspection failed to reveal these spots. The conjunctivas in these cases appeared pale and uniform. The cases belong to the group in which death took place late in the disease, on the twenty-third, forty-second or fifty-sixth day. Death was caused, in these cases, by various complications, such as pneumonia or reactivated pulmonary tuberculosis.

In the majority of typhus cadavers the conjunctival eruption is a characteristic gross sign, which has a definite diagnostic significance. Characteristic of the sign are (1) multiple red spots and dots or points and (2), particularly characteristic, oblong and oval spots. The points and spots present various forms and are dissimilar as regards intensity of bright red or yellow color. These changes are seen on the conjunctiva of the lower lid, the upper lid and occasionally the sclera. The upper lid should be turned out completely for examination.

Gross examination of this sign suggested that the spots are the result of petechial hemorrhages of varying intensity, analogous to the extravasation not infrequently observed in the gastric mucosa in spotted typhus. However, microscopic studies revealed that these changes represent specific typhus lesions of the arteries and capillaries. Pronounced thrombovasculitis is observed with great frequency. The lumens of the arterioles and capillaries and occasionally of the veins are occupied by red hyaline or mixed thrombi. Organized small fibrinous thrombi are encountered frequently. Segments of blood vessels are commonly the seat of fibrinoid necrosis affecting all of the layers of the wall. Vascular endothelium is found to be in a state of proliferation and pronounced swelling. The adventitial cells are increased. Lymphoid and plasmocytic infiltrations sur-

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round many vessels. In addition to the changes of a destructive thrombotic character there are compact nodular formations occasionally surrounding a vessel in a stage of stasis. Small hemorrhages are occasionally noted. The process described develops immediately beneath the epithelial layer of the conjunctiva. The epithelial layer itself presents moderate degenerative changes in the form of vacuolation, pyknosis and desquamation of single cells.

These changes were present with greater or lesser intensity in all of the investigated cases. Destructive thrombotic processes predominated in cases with a short clinical course (eight to ten days). Proliferative changes dominated the picture in cases in which death occurred on the fourteenth to the sixteenth day of the disease. The alterations described are a part of a typical pathologic picture of typhus as described in great detail by Fraenkel,[1] Davidovskiy[2] and Kyrle and Morawetz[3]; the conjunctival lesions are homologues of the roseola and the petechiae regularly observed on the skin of patients with typhus. It is logical, therefore, to refer to these changes as the conjunctival exanthem. The rather frequent mucosal lesions of typhus are the result of hemorrhages not accompanied with specific vascular changes (Ceelen[4]; Davidovskiy[2]). Study of the literature revealed that the sign is not new; Chiari[5] described it in 1917. It appears, however, to have been forgotten. Chiari described oval bluish red spots which appeared on the conjunctivas in typhus even before the roseola of the skin and which remained during the entire convalescence. They may be seen even after the rash has disappeared; in fact, they may be the single sign of a recent occurrence of spotted typhus. Chiari's histologic studies confirmed the identity of the conjunctival and dermal lesions. The work of Chiari, however, aroused little interest in pathologists, ophthalmologists and students of infectious diseases. Most of the textbooks at hand contain no mention of it. In Russian medical literature Chiari's observation was corroborated by Braunshtein[6] in 1919 and was cited by Davidovskiy[2] in his monograph of 1920.

The following questions appear pertinent: 1. Is this sign to be observed in persons dying of other infectious diseases? 2. Is it permissible to make a positive anatomic diagnosis in doubtful cases on the basis of this sign?

In more than 600 cadavers conjunctival spots were encountered with fair constancy in only the following infectious diseases: (1) typhus, (2) septic endocarditis, particularly endocarditis lenta, and (3) meningococcic sepsis. Exceptionally, red spots were noted on the conjunctivas in pneumococcic sepsis complicated by purulent meningitis. Other infectious diseases only rarely present similar changes. The conjunctival changes in the aforementioned diseases present certain more or less characteristic differences. In meningococcic sepsis the spots are few, large and deep red. The well known conjunctival hemorrhages of septic endocarditis are usually larger and brighter and not infrequently contain a grayish center. It seems clear that the finding of the characteristic changes in the conjunctivas of cadavers justifies the suspicion of typhus in clinically obscure cases.

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1. Fraenkel, E.: Die Haut bei der Fleckfiebererkrankung, in Schjerning, O.: Handbuch der ärztlichen Erfahrungen im Weltkriege, Leipzig, J. A. Barth, 1922, vol. 8.

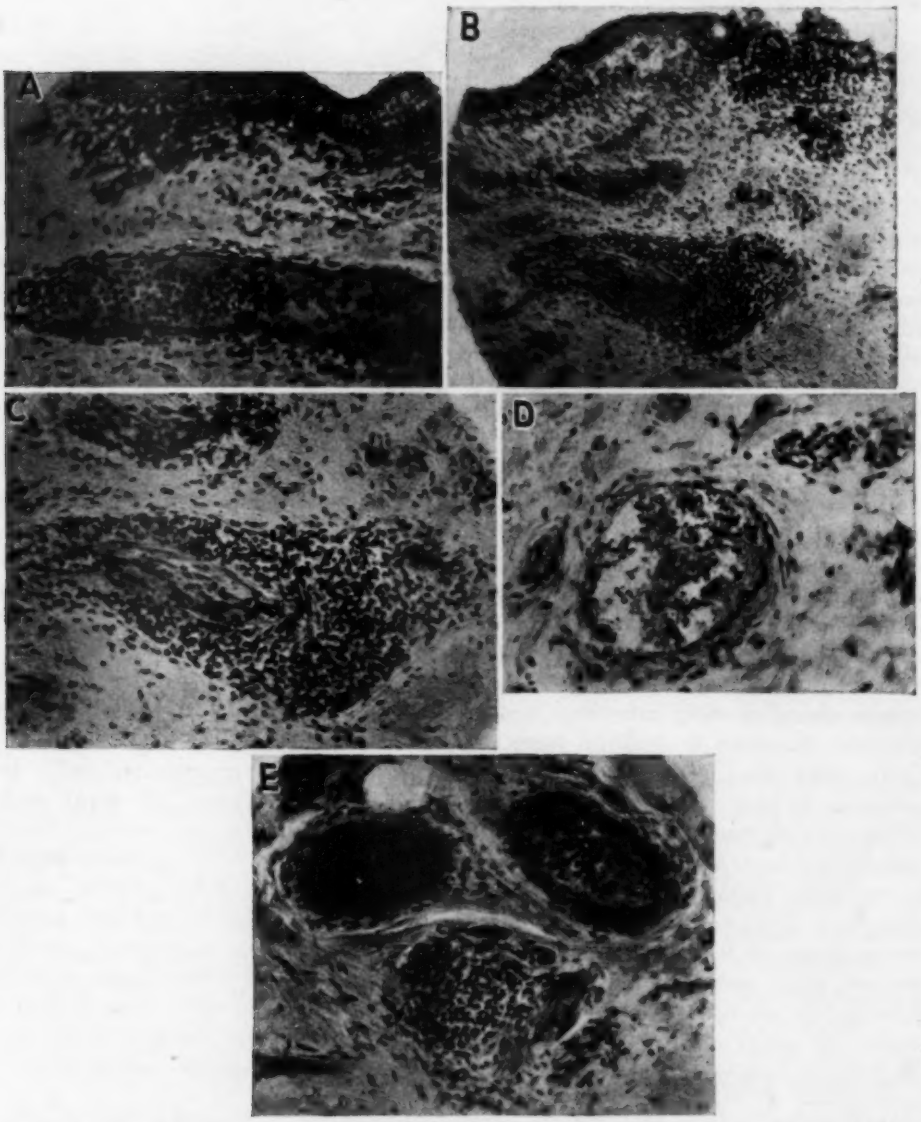
2. Davidovskiy, I. V.: Patologicheskaya anatomya i patologya sipnovo tifa, Moscow, Gosizdat, 1920.

3. Kyrle, J., and Morawetz, G.: Wien. klin. Wchnschr. **28**:1286, 1915.

4. Ceelen, W.: Pathologische Anatomie der inneren Organe bei Fleckfieber, in Schjerning, O.: Handbuch der ärztlichen Erfahrungen im Weltkriege, Leipzig, J. A. Barth, 1922, vol. 8.

5. von Chiari, R. F.: Wien. klin. Wchnschr. **30**:1479, 1917.

6. Braunshtein, E.: Eye Involvement in Spotted Typhus, 1919.



A, thromboendovasculitis immediately below the epithelium of the conjunctival fold on the tenth day of illness. *B*, typical perivascular granuloma and focal necrosis of conjunctival epithelium on the fourteenth day of illness. *C*, the same with greater magnification. *D*, incipient organized vascular thrombosis in the deeper layers of the transitional fold on the fourteenth day of illness. *E*, perivasculitis and endovasculitis and red thrombi in deep sections of the transitional fold on the fourteenth day of illness.

To illustrate the point, 2 cases are described:

1. A man 62 years old presented fever and a cutaneous rash. The Weil-Felix reaction was negative. Death occurred on the eighteenth day. The patient had had typhus in 1918. The clinical diagnosis was typhus. Inspection of the body revealed no cutaneous rash; on the conjunctivas one noted small reddish dots and yellow spots. The spleen weighed 150 Gm. The cerebral meninges were edematous. There was consolidation of the lower lobe, with fibrinous pneumonia in the upper lobe, of the right lung. The conjunctivas presented occasional thrombovasculitis and hemorrhages. The medulla presented multiple typical spotted typhus nodes. The pathologic diagnosis was typhus and lobar pneumonia.

In this case, despite the obscure clinical picture and the history of typhus in the past, the clinicians diagnosed typhus on epidemiologic data, which was confirmed by the conjunctival exanthem, despite the fact that the postmortem examination revealed lobar pneumonia, which could completely account for death.

2. A man 50 years old presented fever and intestinal disturbances. The Weil Felix reaction was negative. There was no rash. Death occurred on the eleventh day of illness. The cadaver presented no traces of an eruption of the skin. Bright red dots and spots were seen on the conjunctivas. The spleen weighed 230 Gm.; the density was increased. The cut surface was deep red with a light grayish tint. The pulp protruded moderately. Degeneration of the liver and of the myocardium, plethora of the brain and edema of the pia mater were also noted. The anatomic diagnosis was typhus. Microscopic studies revealed typical vascular changes and granulomatous nodules in the medulla oblongata. The final pathologic-anatomic diagnosis was typhus.

The clinical opinion leaned more toward the diagnosis of typhoid fever. There did not exist any data for the diagnosis of typhus. Postmortem observations demonstrated the presence of an acute general infectious disease. The conjunctival changes suggested typhus, and the microscopic studies confirmed the suspicion.

Despite the fact that the older clinicians emphasized a particular redness of the conjunctivas in typhus, the conjunctival eruption was unknown to them and is not mentioned in any textbook on infectious diseases. To clarify the question of the presence of this sign in patients, the conjunctivas of a number of persons with typhus were examined and definite red dots and spots were found in only 27 per cent. The sign is much less marked in the living patient than in the cadaver. The reason for this is that there is marked hyperemia of the conjunctiva in typhus and on the red background of the living conjunctiva small red spots are difficult to distinguish. The sign is not necessarily characteristic of the grave cases of typhus. It was observed in a number of patients whose disease was mild and has been seen in convalescents, as originally emphasized by Chiari. It was quite distinct on the eighteenth day of the disease in a man 41 years old. The statement of Chiari with regard to the early appearance of the sign could not be controlled, because of the lack of proper clinical material. In order to eliminate the redness of the conjunctival background, a 1:1,000 solution of epinephrine hydrochloride, 1 drop to 1 cc. of water, has been instilled. So far, no uniform results have been obtained. In only a few cases paling of the conjunctivas revealed the previously unnoticed red dots and spots. The feeble reaction of the conjunctival blood vessels to epinephrine is worthy of notice. According to Rollina,[7] instillation of a solution of epinephrine hydrochloride gives, after two to three minutes, sharp and prolonged paling of normal conjunctivas. In patients with typhus, especially in those with the grave type, the conjunctivas remain unaltered. This is apparently related to the profound vascular loss of tone, which is the basis of the syndrome of typhus. This vascular hypotonia persists

7. Rollina, A.: La circulation conjunctivale, in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 2.

for a long time in convalescing patients. The conjunctival vascular network represents a portion of the peripheral vascular system. Profound hemodynamic alterations peculiar to typhus find their expression in the bright hyperemia of the conjunctivas, which some clinicians erroneously define as conjunctivitis. Because of its accessibility, the vascular network of the conjunctiva presents an exceptional object for clinical physiologic studies. Pharmacologic studies on the conjunctiva may offer an index of the degree of damage to the peripheral circulation. If one wishes to accept the point of view that the symptom of "rabbit's eye" in spotted typhus (redness due to hyperemia) is a partial expression of a cervical syndrome conditioned by a lesion of the upper cervical ganglion, similar experiments will give data for the evaluation of the damage to this most important segment of the vegetative nervous system.

SUMMARY

The aim of this work is to call the attention of pathologists to a gross sign which in its characteristic form justifies the suspicion of spotted typhus even in the absence of clinical data. A final diagnosis in disputed instances can be made only after microscopic study. For the pathologist, of all the localizations of the typhus eruption, the one on the conjunctivas has the greatest significance. It would not be correct to say that the conjunctiva in typhus is affected more than the skin, although in other rickettsial diseases there is definite predilection for certain areas of the skin. Conjunctival alterations in typhus deserve a more intensive clinical and physiologic investigation. They are accessible for immediate observation, and they demonstrate the basic pathologic changes of spotted typhus, namely, the profound functional and anatomic alterations in the peripheral blood vessels.

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN

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Spontaneous or nontraumatic rupture of an otherwise or previously normal spleen is rare. By contrast, nontraumatic rupture of a diseased spleen is not uncommon. Preexisting diseases in cases of the latter may include malaria, leukemia and other blood dyscrasias, typhoid fever, cirrhosis of the liver, splenic infarction, thrombosis of the splenic vein, infectious diseases (including so-called septic spleen), neoplasms and possibly splenomegaly due to various causes. To this list might be added perisplenic adhesions, torsion of the pedicle, subcapsular adhesions and alterations in the consistency of the spleen.

The subject is rendered difficult for several reasons—among them, that the spleen does not lend itself to a concise anatomic description, either gross or microscopic. The dimensions and the weight of the normal spleen vary considerably, and its cellular appearance and composition also vary. Therefore, there are borderline cases in which it can be determined only with the greatest difficulty that the spleen is normal or abnormal.

Examples are numerous. Simple enlargement of the spleen can scarcely be considered a pathologic variation, and yet it may render the spleen more liable to rupture. Furthermore, a splenic lesion may be solitary and comparatively small. Susman [1] pointed out that the spleen may be abnormal in one area only, and if rupture occurs at this point, all evidence of pathologic change is destroyed by the disintegration associated with rupture. Disease in some other organ may or may not have a remote effect on the spleen, and the question may easily arise whether the spleen should be considered normal under such circumstances. The decision whether a ruptured spleen was previously normal or not cannot always be made with certainty.

Likewise, the influence of trauma cannot always be determined. Rupture in this situation may be only apparently spontaneous or subject to individual interpretation. The terms "spontaneous" and "nontraumatic" are not used in a strict sense but rather connote absence of external violence or injury. Some degree of trauma would doubtless be necessary to produce "spontaneous" rupture, but such trauma might be classified as physiologic. This type of trauma might consist of a sudden increase of intra-abdominal pressure, a sudden movement of the spleen or sudden pressure from an adjacent organ or even from gastrointestinal contents amounting to an actual blow. In this category might be placed vomiting, coughing, sneezing, straining, lifting, twisting and jumping. Furthermore, external injury sufficient to rupture the spleen may be so slight as to produce no abrasion, laceration or ecchymosis of the overlying skin; the injury might consist of a fall with the patient landing on the feet or the buttocks; or an injury may be forgotten, considered insignificant or denied by the patient or may have occurred during a period of unconsciousness or of alcoholic intoxication. The intelligence of the patient may be a factor in obtaining accurate information.

Lundell [2] subjected to careful scrutiny 20 cases in the literature which had been designated as instances of spontaneous rupture of the healthy spleen and did not

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1. Susman, M. P.: Brit. J. Surg. **15**:47, 1927.
2. Lundell, G.: Acta chir. Scandinav. **75**:547, 1934.

find a single case which he thought clearly demonstrated that a healthy spleen may rupture spontaneously. He also quoted Lubarsch as denying such an occurrence by stating that a pathologic alteration of the organ is a requisite for the occurrence of a spontaneous rupture. This attitude would appear to be too critical and does not coincide with the experience and belief of the majority of those who have studied the subject.

Several cases have been reported in which a history of slight but probably adequate trauma was elicited days or weeks after operation. In 2 such cases (Jackson [3]; Patey [4]) injury to the left upper part of the abdomen was remembered some time later. Pringle [5] found reports of 5 such cases in the literature. A combination of both of the factors which have been discussed is illustrated in Pringle's case in which the patient was riding a pony at the time of the onset of symptoms, and antemortem thrombosis of the splenic artery and tuberculous splenitis were found. The element of trauma was questionable or slight, and the splenic disease was not readily apparent to the surgeon.

To render the subject still more complex, traumatic rupture of the spleen may be both "acute" and "subacute"; i. e., a latent period may exist between the injury and the occurrence of massive hemorrhage. This has been referred to as a "two stage" rupture of the spleen. The initial injury may cause slight laceration of the capsule accompanied by minimal hemorrhage, to be followed by a subsequent large tear and more extensive hemorrhage. This latent or symptomless period may last from a few hours to a few days and even for weeks. If the injury was slight or remote and the interval of appreciable length, such an incident might not be included in the original history of the case.

The actual incidence of spontaneous rupture of the normal spleen is difficult to determine, chiefly for the reasons enumerated. The literature has been reviewed periodically, and the reported cases have been subjected to critical evaluation. This has been difficult for several reasons, among which is the fact that some authors fail to include a complete description of the gross and microscopic appearance of the spleen. In the accompanying table are listed the reported cases which appear authentic. All of the cases encountered in the literature have been considered, and certain ones have been eliminated. It should be emphasized that such an attempt at evaluation of cases reported by other authors is hazardous and subject to error because of the degree of personal opinion which must be applied.

In 1930 the subject was reviewed by both Bailey [6] and Byford.[7] Bailey collected 11 cases and reported 1 of his own. Of the 11 cases which he collected, there was a delayed history of trauma in 2 (Patey [4]; Jackson [3]), and Ogilvie's and Pyrak's cases were instances of rupture of the splenic vein. This would reduce Bailey's total number of cases to 8. Byford included only 2 of the cases listed by Bailey (Rhame [8]; Susman [1]) but added 4 others (Shorten [9]; Connors [10]; Metcalfe and Fletcher [11]; Skerritt [12]). In 1937 Zuckerman and Jacobi [13] reviewed the literature and objected to accepting several of the cases included in the accompanying table:

3. Jackson, T. S.: Surg., Gynec. & Obst. **41**:331, 1925.
4. Patey, D. H.: Brit. M. J. **1**:898, 1929.
5. Pringle, S.: Irish J. M. Sc., 1931, p. 329.
6. Bailey, H.: Brit. J. Surg. **17**:417, 1930.
7. Byford, W. H.: Arch. Surg. **20**:232, 1930.
8. Rhame, J. S.: Ann. Surg. **88**:212, 1928.
9. Shorten, W. W.: Brit. M. J. **2**:844, 1919.
10. Connors, J. F.: Ann. Surg. **74**:1, 1921.
11. Metcalfe, R. F., and Fletcher, L. Z.: Ann. Surg. **75**:186, 1922.
12. Skerritt, E. M.: Brit. M. J. **2**:641, 1878.
13. Zuckerman, I. C., and Jacobi, M.: Arch. Surg. **34**:917, 1937.

those of (*a*) Skerritt,[12] Connors,[10] Metcalfe and Fletcher,[11] Capecchi,[14] Nixon,[15] Abell[16] and Galloway[17] because a complete pathologic examination of the spleen had not been made; (*b*) Stretton's[18] case because there had been coitus just before the rupture; (*c*) those of Susman[1] and Bohler[19] because each patient was bending to lift a heavy object; and (*d*) Underwood's[20] case because there were perisplenic adhesions and pigmentation of the spleen. Zuckerman and Jacobi[13] agreed with Byford[7] in refusing to consider Atkinson's[21] case authentic. The case reported by Smith, Morrison and Sladden[22] was that of a pregnant woman. Elimination of cases to which there might be valid objection would reduce the number of cases in the table from 35 to 24, and this places the table in the light of being too liberal.

On the assumption that a normal spleen never ruptures spontaneously, there has been speculation as to what deviation from normal might be present before rupture. Susman[1] mentioned four possibilities: (*a*) softening of the spleen and capsule, (*b*) congestion of the portal vein, (*c*) formation of a subcapsular hematoma due to enlargement and (*d*) perisplenic adhesions. Lundell[2] suggested loosening or destruction of the parenchyma of the spleen as the result of generalized or local

Cases of Spontaneous Rupture of the Normal Spleen Previously Reported

Case	Year	Author	Case	Year	Author
1	1874	Atkinson[21]	19	1933	Bohler[19]
2	1878	Skerritt[12]	20	1933	Abell[16]
3	1919	Shorten[9]	21	1933	Smith, Morrison and Sladden[22]
4	1921	Connors[10]	22	1934	Dahle, M.: Acta chir. Scandinav. **75**: 519, 1934
5	1929	Metcalfe and Fletcher[11]	23	1934	Basso, R.: Gior. veneto di sc. med. **8**: 275, 1934
6	1922	Metcalfe and Fletcher[11]	24	1935	Burnett, E. C., and McMenemey, W. H.: Brit. M. J. **1**: 1122, 1935
7	1925	Capecchi[14]	25	1935	Young, R. H.: Ann. Surg. **101**: 1389, 1935
8	1926	Stretton[18]	26	1935	Galloway[17]
9	1927	Susman[1]	27	1935	Thomas, G. B.: Brit. M. J. **2**: 1100, 1935
10	1928	Rhame[8]	28	1936	Sjøstrom, P. M.: Chirurg. **8**: 721, 1936
11	1929	Underwood[20]	29	1937	Zuckerman and Jacobi[13]
12	1929	Harvey, T. W., Jr.: J. A. M. A. **93**: 987, 1929	30	1939	Coleman, A. H.: Brit. J. Surg. **27**: 173, 1939
13	1930	Bailey[6]	31	1939	Von Soos, J.: Deutsche Ztschr. f. d. ges. gericht. Med. **31**: 12, 1939
14	1930	Byford[7]	32	1939	Chi, C. K.: Chinese M. J. **56**: 374, 1939
15	1931	Nixon[15]	33	1940	Shafir, L. E.: Vestnik khir. **60**: 574, 1940
16	1932	Kaspar, M.: Beitr. z. klin. Chir. **156**: 97, 1932	34	1940	Tagibekov, K. G.: Vestnik khir. **60**: 312, 1940
17	1933	Black, J. M.: Brit. J. Surg. **20**: 526, 1933	35	1943	Bueermann, W. H.: U. S. Nav. M. Bull. **41**: 73, 1943
18	1933	Halliwell, A. C.: Brit. M. J. **1**: 919, 1933			

infections, circulatory disturbances or necrosis and pointed out that the vulnerability of the spleen is increased when the organ is enlarged or abnormally mobile because of the overdistention of the capsule and because part of the spleen may no longer be protected by the costal arch.

REPORT OF A CASE

A 35 year old Negro was admitted to the City of Detroit Receiving Hospital Feb. 9, 1930. On the morning of admission he began to have a dull aching pain in the left lower part of the chest anteriorly. This pain became more severe within a half hour—so sharp that he could not stand upright. The pain moved downward toward the umbilicus and radiated to the lower part of the abdomen, particularly to the left lower quadrant. He was nauseated and attempted to vomit but without success. He took magnesium sulfate and had two bowel

14. Capecchi, E.: Policlinico (sez. prat.) **32**:665, 1925.
15. Nixon, P. J.: J. A. M. A. **96**:1767, 1931.
16. Abell, I.: Ann. Surg. **98**:722, 1933.
17. Galloway, W. D.: Brit. J. Surg. **23**:235, 1935.
18. Stretton, J. L.: Brit. M. J. **1**:901, 1926.
19. Bohler, E.: Bull. Soc. d'obst. et de gynéc. **22**:707, 1933.
20. Underwood, W. E.: Brit. M. J. **1**:1118, 1929.
21. Atkinson, E.: Brit. M. J. **2**:403, 1874.
22. Smith, A. H. D.; Morrison, W. J., and Sladden, A. F.: Lancet **1**:694, 1933.

movements. On admission the pain was more severe in the left lower part of the chest anteriorly.

The patient's past history was unimportant except for childhood diseases and three attacks of gonorrheal urethritis, the last one three months prior to admission. After heavy work he sometimes had abdominal pain, which was associated with a right inguinal hernia descending into the scrotum. He was never constipated. There had been no operations. His family history seemed irrelevant. His occupation was that of a carpenter. He was a fairly heavy consumer of alcoholic beverages up to seven or eight months before this illness.

Examination by systems gave essentially negative results, except that of the chest and the abdomen. The contour of the chest was normal; inspiratory excursion was limited on the left side, particularly in the lower half. Breath sounds were diminished in the left lower lung field posteriorly, and a few moist, rather coarse rales were heard in the same area. Resonance was impaired and voice sounds were diminished over the lower lobe of the left lung. Tenderness in the left upper quadrant of the abdomen and in the right inguinal area was marked. The abdomen was soft. There was slight tenderness in the left costovertebral angle. A right inguinal hernia was present, which was quite sensitive on insertion of the finger into the ring. There was no elevation of temperature.

Fluoroscopic examination of the chest February 10 revealed both lung fields clear with marked diminution in the excursion of both sides of the diaphragm. The left leaf of the diaphragm was slightly higher than normal. There was no evidence of pneumothorax, and no air was observed under either leaf of the diaphragm. The hemoglobin content was 60 per cent. Erythrocytes numbered 4,100,000 and leukocytes 15,000 per cubic millimeter, and polymorphonuclear neutrophils 65 per cent. The urine had a specific gravity of 1.022, with a trace of albumin and occasional leukocytes and red blood cells. The suggestions for a provisional diagnosis did not include rupture of the spleen.

Laparotomy was performed February 11 by Dr. Charles C. Lakoff. The abdomen contained a large amount of blood. The left upper quadrant was explored, and the spleen was found to be ruptured, hemorrhage occurring most profusely from the hilus. The spleen was removed.

The spleen weighed 130 Gm. There was a linear tear through the capsule extending from the hilus to the margin and onto the convex surface. A clot of blood was adherent to the laceration. When sectioned, the parenchyma seemed to be somewhat engorged. Microscopic examination revealed no outstanding tissue changes. In the vicinity of the laceration there was some hemorrhagic extravasation but no evidence of necrosis or infection. The sinuses were not engorged. The smaller branches of the splenic artery were moderately sclerotic. The capsule and the trabeculae were of normal thickness. Fibrosis was absent.

The patient's progress following operation was not unusual. His anemia lessened, and the leukocytosis gradually disappeared. On the ninth postoperative day healing of the wound was satisfactory. On the fourteenth day the patient was up and about the ward, and on the following day he was discharged from the hospital. During his convalescence he was carefully questioned several times regarding any injury he might have received prior to the onset of symptoms. He persistently denied even a slight injury to the left side of the body from either a blow or a fall. He was cooperative and intelligent, and it was finally concluded that all reasonable possibility of trauma could be excluded.

SUMMARY

Spontaneous rupture of a previously normal spleen is a rare lesion, the exact incidence of which is difficult to determine. While such an entity doubtless exists, a certain amount of suspicion is always attached to the diagnosis because the spleen may not have been exactly normal previously and because the elimination of the possibility of minor trauma is difficult.

While the subject easily lends itself to controversy, and criteria for establishing a diagnosis are not concise, a definition of the disease is necessary. Accordingly, the following definition is proposed: The diagnosis spontaneous rupture of the normal spleen means that the spleen on careful pathologic examination is found to be free from disease and that no history of injury can be elicited other than the movements or physiologic strains which are a part of the daily life of the average person.

On the basis of liberal criteria, 35 cases have been collected from the literature. That a few additional cases may have been overlooked or a few questionable cases included is admitted.

An obviously authentic case is added.

MORPHOLOGY OF THE EASTERN AND WESTERN STRAINS OF THE VIRUS OF EQUINE ENCEPHALOMYELITIS

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For several years, studies have been in progress on the purification and the properties of the Eastern and Western strains of the virus of equine encephalomyelitis. The application of ultracentrifugal procedures to extracts of chick embryos diseased with the Eastern strain has resulted in the isolation [1] of an essentially monodisperse liponucleoprotein complex behaving biologically as the virus. Similar investigations [2] made with the Western strain have shown that this agent is likewise a liponucleoprotein complex. Recently the electron microscope has been used in the direct examination of purified preparations of the two strains of virus. Electron micrographs providing information on the size, shape and morphologic structure of the virus particles previously reported briefly [3] are described in the present paper.

MATERIAL AND METHODS

The purified preparations of the virus of equine encephalomyelitis were obtained by ultracentrifugation of virus-infected chick embryo material. The sequence of the cultivation of the Eastern strain of the virus in the embryo, the extraction of the tissue and the ultracentrifugal procedures have been described.[1] In 1 instance the virus was obtained by ultracentrifuging the chorioallantoic fluid from diseased embryos. The purified Western strain [2] of the virus was obtained by procedures similar in general to those employed for the Eastern strain. Details will be reported in a subsequent publication.

The purified viruses are relatively stable in Ringer solution,[4] which has been used for extracting the embryo tissues and for dissolving the purified material. For examination in the electron microscope, Ringer fluid containing the virus was diluted to a virus concentration of about 0.5 mg. per cubic centimeter and placed on the thin collodion film with a fine pipet. Excess liquid was removed from the film after a few seconds with the same pipet and the remainder allowed to dry. In some cases the diluent was water, and in others various salt solutions were used. In the latter cases some definite interval of time was allowed to elapse between dilution of the original sample with the new salt solution and preparation of the film. Salt was sometimes removed from the dried preparations by lightly washing them with water from a fine pipet or by dipping the screen and collodion film in water several times. Usually the films were not washed at all.

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1. Taylor, A. R.; Sharp, D. G.; Beard, D., and Beard, J. W.: J. Infect Dis. **72**:31, 1943.

2. Taylor, A. R.; Sharp, D. G.; Beard, D., and Beard, J. W.: To be published.

3. Taylor, A. R.; Sharp, D. G.; Beard, D., and Beard, J. W.: Proc. Soc. Exper. Biol. & Med. **51**:332, 1942. Sharp, D. G.; Taylor, A. R.; Beard, D., and Beard, J. W.; ibid. **51**: 206, 1942.

4. Bayliss, W. M.: Principles of General Physiology, ed. 4, London, Longmans, Green & Co., Ltd., 1927.

The electron microscope[5] was the RCA type B, and all micrographs were made with 55 kilovolt electrons. The exposures were made at a magnification of 15,700 times on a plate field 2 inches (5 cm.) square, and the desired enlargement for greater magnification was made photographically from this plate. The magnification was based on measurements of the width of tobacco mosaic rods, which has been reported to be 15 millimicrons.[6]

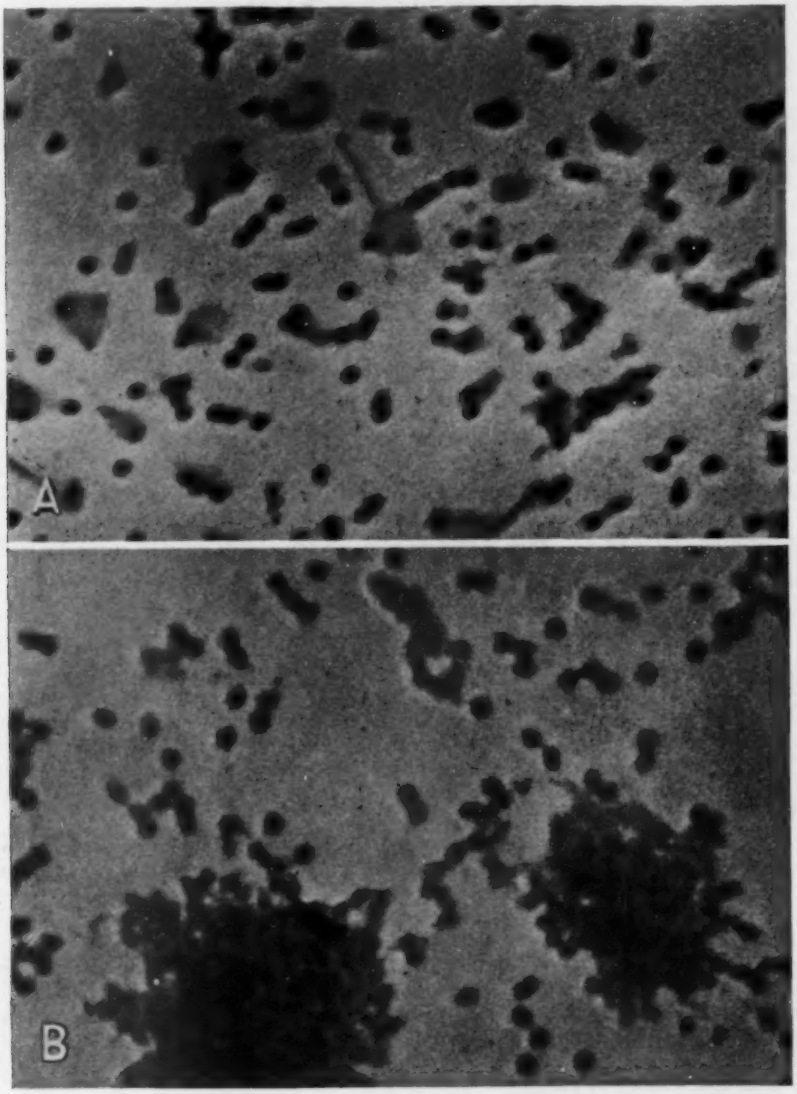

Fig. 1.—*A*, Eastern strain, and *B*, Western strain of the virus of equine encephalomyelitis. Suspensions in Ringer solution were diluted with water for preparation of the electron microscope films. × 45,000.

ELECTRON MICROGRAPHY

In the initial experiments the Ringer fluid preparations of the virus were diluted with water in varying proportions, usually about 1 to 5, resulting in a final salt concentration of about 0.03 molar. The film was then prepared and

5. Hillier, J., and Vance, A. W.: Proc. Inst. Radio Engin. **29**:167, 1941.
6. Stanley, W. M., and Anderson, T. F.: J. Biol. Chem. **139**:325, 1941.

examined without subsequent washing. In figure 1 are shown a micrograph of the Eastern strain (*A*) and one of the Western strain (*B*) made within a few hours after purification. The images of the respective strains shown in figure 1 are similar in general appearance, and, as will be seen in succeeding micrographs, no definite character differentiating the two strains is observed. In the respective micrographs, taken at 15,700 diameters and enlarged photographically to 45,000 diameters, the predominant images are remarkably uniform in size and shape, and of relatively low contrast, especially at the periphery. Individual images in both figures reveal definite indications of an internal structure or differentiation of material within the particles, which appear to be constituted in general of two substances, the one situated wholly within the other. The inner region is seen as a well defined structure of greater density than the enveloping material. In these fresh preparations the denser structure is approximately centrally placed and appears to be about one third of the total diameter of the particle. Its shape

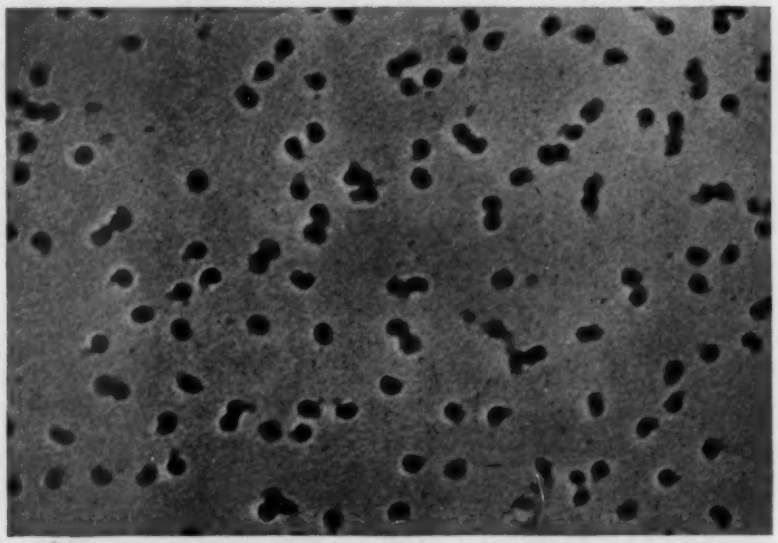

Fig. 2.—Electron micrograph of the Western strain shown in figure 1 *B* after sixteen days. The virus in Ringer solution was diluted with Ringer solution for preparation of the electron microscope film. × 45,000.

in general is round, and the density appears uniform. In individual particles, the outer less dense enveloping material, though of low density, seems well defined as by a limiting structure. When particles are adherent, this outer substance seems sticky and easily deformed, stretching between particles in short narrow or broad strands.

A micrograph obtained sixteen days after the isolation of the Western strain shown in figure 1 *B* is given in figure 2. In this older preparation certain of the chief characters seen with the fresh virus are preserved. Compared with the fresh preparation, however, the older one shows far greater contrast and definition and reveals marked variations both in the internal denser structure of the particle and in the surrounding material. Most of the particles, as judged by the images, have lost the round form and have become comma shaped, with the denser internal structure forming the head. In many images the tail piece appears sickle shaped; in others it is a broad-based conical structure which gives to the whole image

the appearance of a falling drop of fluid. The tail piece is of considerably lower density than the rounded head, and for the most part, especially the conical forms, the density grades progressively toward the periphery.

The Western strain preparation of figure 1 *B* was titrated for infectivity in 3 week old mice at the time the micrograph was made, and again after sixteen days,

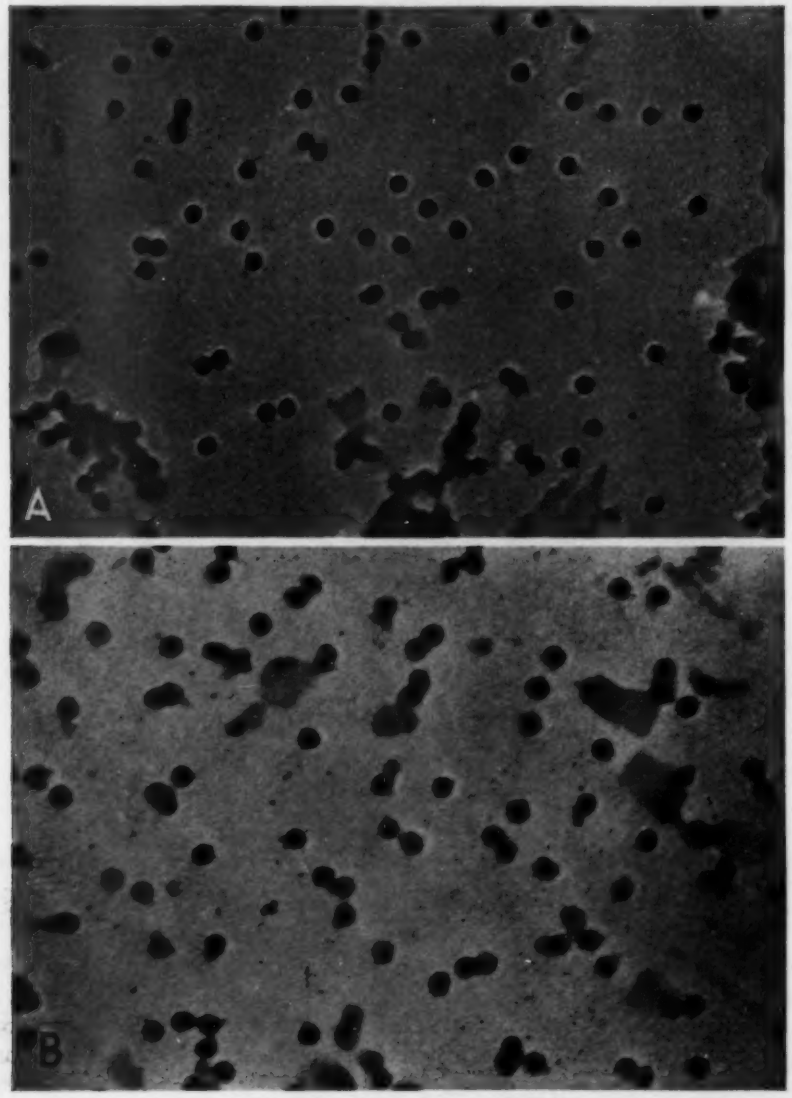

Fig. 3.—Eastern strain, *A*, and Western strain, *B*, treated with 0.023-molar calcium chloride. × 45,000.

when figure 2 was obtained. During the sixteen day interval the infectious titer diminished about three decimal dilutions, indicating inactivation of approximately 99.9 per cent of the virus originally present. Practically, then, the images of figure 2 are those of noninfectious virus particles. There was no change in the character of the sedimentation diagram or the sedimentation constant associated with this loss of infectivity.

The micrographs described in the foregoing paragraphs were made from films of virus in Ringer solution diluted with water. With this sort of material good micrographs were obtained infrequently, owing primarily to the relatively low contrast of the images and to the irregular distribution of particles on the film. In addition the images were seen in much smaller numbers than would be expected on the basis of the amount of virus present as determined by chemical means. A method for increasing contrast and dispersion of the images was found in the treatment of the virus with calcium chloride before preparation of the collodion film. For this procedure the virus was dissolved in Ringer solution in the usual way. The preparations were diluted with solutions of calcium chloride of various concentrations and allowed to stand for varying intervals and then pipetted on films.

Figure 3 *A* shows the micrograph of the Eastern strain treated with 0.023 molar calcium chloride solution and allowed to stand for one hour. The marked effects of the calcium salt are seen in the uniform distribution of the images in the field and in the greater contrast of the images, especially at the periphery. The Western strain (fig. 3 *B*) prepared in a similar manner shows like effects of calcium chloride. A greater effect of the salt in higher concentration, 0.092 molar, is revealed for the Eastern strain and for the Western strain in figure 4 *A* and *B*.

The differentiation in internal structure of the Western strain is clearly shown in figure 3 *B*, where the inner denser area is distinctly outlined against the surrounding envelope of lower density. The internal structure of the Eastern strain is particularly well illustrated in figure 5, which is a micrograph of the virus sedimented from the chorioallantoic fluid of embryos infected with the virus. The chorioallantoic membranes of chick embryos were inoculated in the usual way. When the embryos were harvested the chorioallantoic fluid was aspirated with a syringe and needle. The virus was sedimented by spinning the fluid at 40,000 g (i. e., 40,000 times gravity) for one hour, and the sediment, taken up in Ringer fluid, was diluted with a 0.023-molar calcium chloride solution. In the micrograph of this partially purified virus preparation there are present relatively large, uniformly circular images of the virus surrounded by much amorphous material and small particles approximately 5 to 15 millimicrons in diameter. The action of the calcium chloride was just sufficient to enhance the contrast at the periphery without obscuring the internal structure, which is clearly revealed as a uniformly round dense area centrally located in the image.

Effects on contrast and distribution such as those produced by calcium chloride were not seen with sodium or potassium chloride similarly used. Further, the action of calcium chloride was definitely related to time and salt concentration. Neither contrast nor distribution was affected when the films were made immediately or within a few minutes after the addition of calcium chloride. The best results were obtained after the preparation had stood for one hour at room temperature in calcium chloride of about 0.023-molar concentration. At 0.092-molar concentration the contrast was usually so great that the character of the images was obscured, as it is, to some extent, in figures 4 *A* and *B*. When preparations of virus treated with calcium chloride were washed, either by pipetting water onto the dried film or by dipping the film into water, one or several times, the effect was destroyed, and the images were of low contrast, as if the initial dilution had been made with water instead of calcium chloride.

VIRUS PARTICLE SIZE

Studies were made of the particle size of the Eastern and Western strains of the virus by measurements of image diameters in the electron micrographs. Rela-

tively wide differences were observed in the values obtained from various preparations dependent, apparently, on the technic involved in preparing the material for micrography. In micrographs of fresh preparations diluted with water the contrast at the periphery of the image was so low, as illustrated in the micrographs of figure 1 *A* and *B*, that measurements of the diameter were indefinite. With the increase

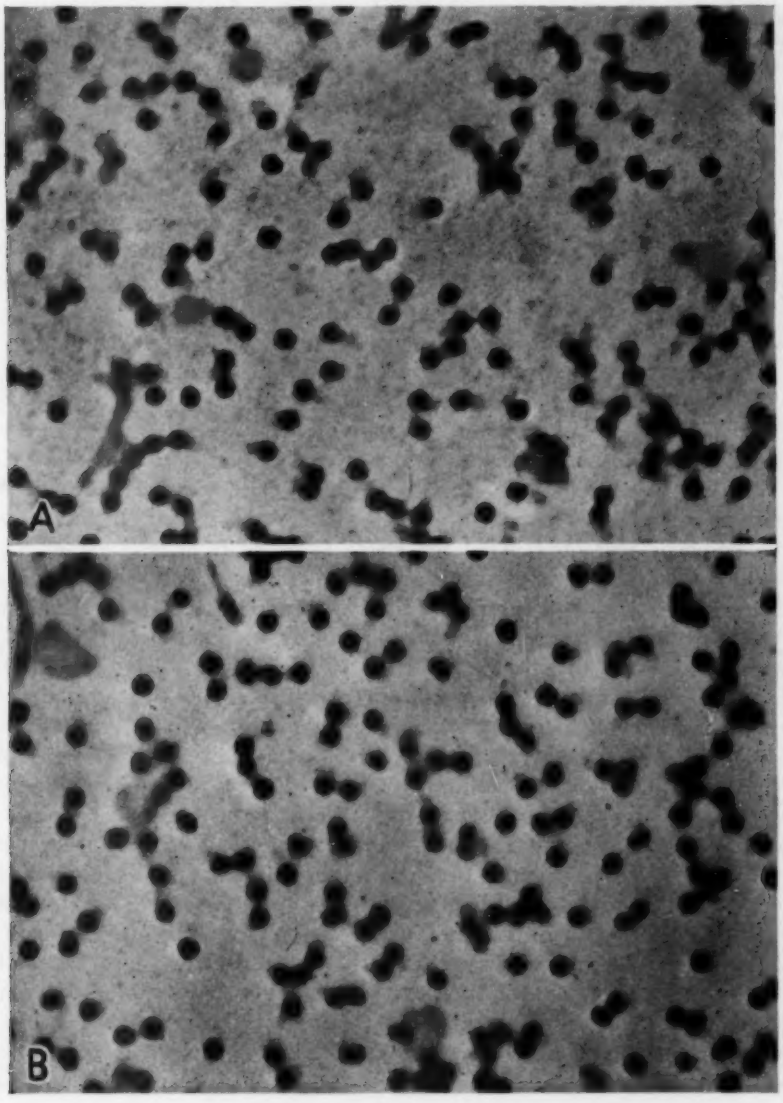

Fig. 4.—Eastern strain, *A*, and Western strani, *B*, treated with 0.092-molar calcium chloride. × 45,000.

in contrast due to calcium chloride, the particle limits became distinct, and the measurability of diameters was increased. The values obtained in measurements on several preparations treated by various technics for electron micrography are given in the accompanying table, in which each value is the average of 20 images.

The average diameter for the two preparations of the Eastern strain diluted with water, in which calcium chloride was present in concentrations less than

0.011-molar, was 42.2 millimicrons. On treatment of the virus with 0.023-molar to 0.092-molar calcium chloride, the average diameter was generally increased, resulting in 1 instance in a value of 58.3 millimicrons for a preparation treated for one hour with 0.092-molar calcium chloride.

The findings with the Western strain were very similar to those with the Eastern strain. The average diameter of virus particles in preparations diluted with water was 39.6 millimicrons, and the maximum with calcium chloride was 58.8 millimicrons, the pictures showing the same general characteristics.

With both strains of the virus, the micrographs showing the best contrast while retaining internal detail in the particle images, whether this was obtained with

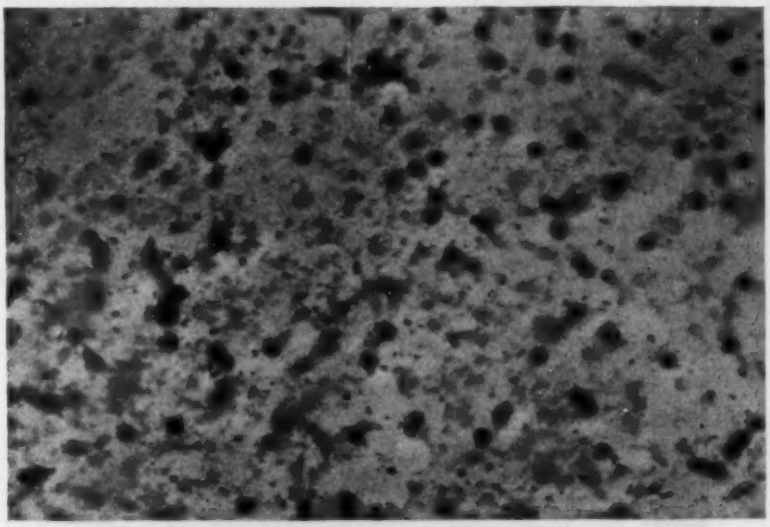

Fig. 5.—Eastern strain partially purified from chorioallantoic fluid. The final concentrate in Ringer solution was treated with 0.023-molar calcium chloride. × 45,000.

TABLE 1.—*Diameters of Particles of Eastern and Western Strains of the Virus of Equine Encephalomyelitis Measured in Electron Micrographs of Preparations Treated in Various Ways (See Text)*

Preparation *	Diluent	Treatment	Mean Diameter, Millimicrons †
EE 96	Water	Unwashed	40.2
EE 96	Water	Unwashed	44.1
EE 100 ‡	0.023 molar $CaCl_2$	Unwashed	47.4
EE 99	0.023 molar $CaCl_2$	Unwashed	47.5
EE 98	0.023 molar $CaCl_2$	Unwashed	53.6
EE 99	0.092 molar $CaCl_2$	Unwashed	53.9
EE 98	0.092 molar $CaCl_2$	Unwashed	58.8
WS 78	Water	Unwashed	39.6
WS 108	Water	Unwashed	41.9
WS 90	Ringer solution	Unwashed	39.3
WS 102	Ringer solution	Unwashed	38.0
WS 102	Ringer solution	Unwashed	42.2
WS 110	0.011 molar $CaCl_2$	Severely washed	38.3
WS 110	0.011 molar $CaCl_2$	Unwashed	57.9
WS 110	0.023 molar $CaCl_2$	Unwashed	55.5
WS 102	0.023 molar $CaCl_2$	Unwashed	57.3
WS 108	0.092 molar $CaCl_2$	Washed	44.3
WS 102	0.092 molar $CaCl_2$	Lightly washed	58.3
WS 103	0.092 molar $CaCl_2$	Unwashed	58.9
WS 103	0.092 molar $CaCl_2$	Washed	58.1

* EE = eastern strain; WS = western strain.
† Each value represents the mean of measurements on 20 particles.
‡ This was virus purified from chorioallantoic fluid.

0.023-molar calcium chloride without washing or with 0.092-molar calcium chloride and subsequent light washing, gave average diameters of about 47.5 millimicrons for the Eastern strain and 53.1 millimicrons for the Western strain.

HOMOGENEITY OF THE VIRUS PREPARATIONS

The present findings provide information not only as to the appearance of the virus particles but also as to the homogeneity of the virus preparations and the nature and the quantity of extraneous material that may be carried along in the process of purification. Before access to the electron microscope, the chief means for judging the degree of homogeneity was a study of the sedimentation velocity patterns obtained with the ultracentrifuge. Data obtained in this way indicated that the purified preparations of Eastern and Western strains were highly homogeneous. The sedimentation diagrams of the Eastern and Western strains are shown in figure 6 *A* and *B*. The respective diagrams reveal a single sharp boundary characteristic of a monodisperse system. Possible contaminants of the purified preparation are the light tissue proteins of normal chick embryo, too small

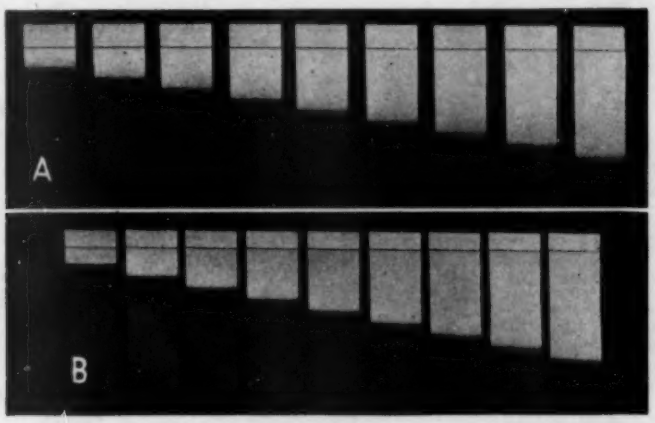

Fig. 6.—*A*, sedimentation diagram of the Eastern strain. *B*, sedimentation diagram of the Western strain. The exposures were made at intervals of two and one-half minutes in a mean centrifugal force field of 17,000 g.

for sedimentation in the ultracentrifugal field employed for purification, and the normal macromolecular chick embryo component, which occurs also in the diseased embryo. The light tissue proteins of low molecular weight are regularly discarded in the supernatant fluid after sedimenting the virus at 30,000 g for one hour. The chief difficulty in purifying preparations of both Eastern and Western strains, however, has been the presence of the macromolecular component,[7] which has a sedimentation constant of $S_{20^\circ} = 78.7 \times 10^{-13}$. This component when present with the virus in sedimented preparations is seen as a second boundary above that of the virus. In figure 6 *A* and *B* there is no evidence of a second boundary nor is there a general absorption of light above the primary virus boundary that might be attributed to the very small tissue proteins.

The evidence of homogeneity of the purified virus preparation provided by the sedimentation velocity studies is substantiated by the electron micrographs. While extraneous material, most of which was apparent as amorphous shadows, is seen in figures 1 to 4, it was small in quantity in comparison with the number

7. Taylor, A. R.; Sharp, D. G.; Beard, D., and Beard, J. W.: J. Infect. Dis. **71**:115, 1942.

of virus particles present. It should be emphasized that none of the films giving these micrographs was washed. The material seen, therefore, represents the whole quantity of virus and extraneous substance present in the fluid that was allowed to dry on the film.

Of especial interest was the relative freedom of the preparations from the macromolecular component of normal chick embryo tissue. This component, purified by ultracentrifugation, has been studied with the electron microscope, and a micrograph of it at the same magnification as the virus pictures of figures 1 to 4 is given in figure 7. As indicated by the images, the particles of the component appear to be approximately spherical, with a diameter of about 20 millimicrons. Though of low density and not well resolved, the particles would be expected to be revealed, if present, in micrographs of the virus preparations of comparable magnification. Small particles of about this or smaller size are seen in profusion in the partially purified preparation of figure 5. The exceedingly small number of

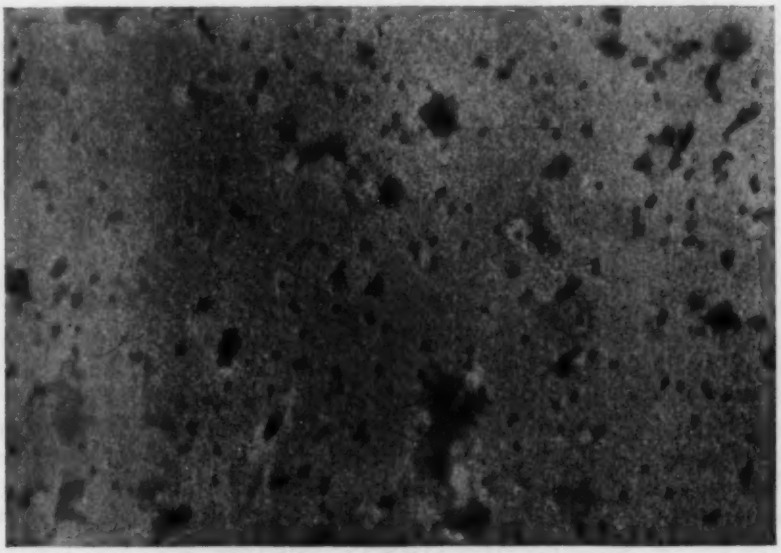

Fig. 7.—Macromolecular component of normal chick embryo tissue. × 45,000.

particles of 20 millimicrons diameter in figures 1 to 4 confirms the evidence of homogeneity of the virus preparations furnished by the sedimentation diagrams of figure 6 *A* and *B*.

COMMENT AND SUMMARY

Electron micrographs of freshly purified Eastern and Western strains of the virus of equine encephalomyelitis showed regularly the presence of circular images of uniform size indicating a spherical shape for the particles producing the images. In the images of both strains there was seen differentiation in internal structure, which was evident in the presence of a circular and relatively dense area centrally located and about one third of the total diameter of the image. Little evidence was seen of material other than that responsible for the circular images, a finding substantiating the indications of monodispersity furnished by sedimentation velocity diagrams.

When the purified virus in Ringer solution was diluted with water for preparation of the electron microscope film, the contrast of the resulting images was

low and their limits were indistinct. The diameters of the particles measured from these indefinite images averaged about 42 millimicrons for the Eastern strain and about 39 millimicrons for the Western strain. With the increased contrast near the periphery of the images obtained on treatment of the virus preparation with calcium chloride in optimum concentration, the diameters of the particles averaged approximately 47 millimicrons for the Eastern strain and 53 millimicrons for the Western strain. Inasmuch as the image size differed considerably with the conditions of micrography, it was difficult to assign a definite dimension to the virus from measurements of images. There was no *a priori* reason why measurements of the pale diffuse images obtained in water, in which the virus is known to be unstable, would indicate more nearly the true dimensions than those obtained after treatment with 0.023-molar calcium chloride. Under the latter conditions, the sharply outlined images could be measured more accurately, yielding values with a smaller variation for a given preparation than the images of low contrast.

The sedimentation constant of the Eastern strain [1] is $S_{20^\circ} = 273 \times 10,^{-13}$ and the specific volume is 0.839. For the Western strain [2] the respective values are $S_{20^\circ} = 265.5 \times 10^{-13}$ and 0.864. From these data, assuming that the particles of the two strains of virus are spherical, as repeatedly indicated by the circular images of uniform size in the electron micrographs, we find that the diameter of the Eastern strain particle is 50.4 millimicrons and that of the Western strain 56.8 millimicrons. These values are not greatly different from those obtained through direct measurement of the images of the particles after treatment with 0.023-molar calcium chloride.

A finding of great practical value, somewhat analogous to the utilization of salts of heavy metals for selective staining of bacteria [8] in electron micrography, was the usefulness of calcium chloride for studies with the electron microscope on the virus of equine encephalomyelitis and more recently [9] the influenza A virus. In the instance of the virus of equine encephalomyelitis the action of calcium chloride was doubly useful in increasing the image contrast at the periphery and in providing a uniform distribution of images in the electron microscope field. These effects occurred regularly when a 0.023-molar to 0.092-molar calcium chloride solution was used and the virus was allowed to stand at room temperature for one hour before the microscopic films were prepared. Although the even distribution of the images was an advantage in micrography, the increased contrast of the images was the best feature, for it is not so much the smallness of the image but its low scattering power for electrons that makes this virus difficult to photograph in detail. Some increase in size of image occurred with use of the salt, but no change was observed in the sedimentation constant of the treated virus. It is unlikely that the changes in contrast occurred entirely at the moment of drying of the film, for such changes would be expected to take place irrespective of the time between dilution and preparation of the dried film. The virus material is a lipoprotein, and particles of this nature might acquire calcium in solution sufficient to increase particle contrast without causing detectable change in the sedimentation constant, for calcium has an atomic number much higher than that of any major element of the particle's constituents. Such an adsorption of calcium or reaction might be selective in the case of a lipoprotein, a possibility suggested by the fact that neither the images of the papilloma virus nor those of the tobacco mosaic virus are affected by the use of calcium chloride.

8. Mudd, S., and Anderson, T. F.: Exper. Med. **76**:103, 1942.

9. Taylor, A. R.; Sharp, D. G.; Beard, D.; Beard, J. W.; Dingle, J. H., and Feller, A. E.: J. Immunol., to be published.

ADENOACANTHOMA OF THE PYLORIC END OF THE STOMACH

A CONSIDERATION OF ITS HISTOGENESIS AND A REPORT OF TWO CASES

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Among reports concerning thousands of cases of carcinoma of the stomach from the standpoint of histology there are described only 7 pyloric tumors in which a combination of adenomatous and epidermoid characteristics was observed. Squamous cell carcinoma of the stomach is rare—a total of 19 cases being found recorded in the literature. In 11 of these the neoplasm was limited to the pyloric end of the stomach (tables 1 to 4). It is significant that of the 11 cases of squamous cell carcinoma of the pyloric area reported to date, 7 are cases of the mixed adenoacanthomatous type. One's interest in this rare type of tumor is further intensified by the fact that heteroplastic squamous epithelium in the pyloric region is practically unknown. Oberling,[1] however, observed a newborn infant, dead of acute ulcers of the stomach, in whom islets of esophageal mucosa were strewn along the lesser curvature of the stomach to the pyloric region.

The occurrence of heterologous mixed squamous cell adenocarcinoma in the pyloric portion of the stomach raises interesting questions referable not only to normal and abnormal structural development but also to the possible role of metaplasia as well as to that of a multipotent response resulting from stimulation of undifferentiated "basal" cells. In the absence of heteroplastic squamous epithelium, how does one or how may one account for the acanthomatous component in such tumors? Does metaplasia play a role in their histogenesis? May direct stimulation of undifferentiated "basal" cells in the mucosa result in polymorphous structures, or are there "embryonic rests" from which heterologous tumors arise? The evidence for and against these various possibilities is both clinical and experimental. It is my view that most of the evidence favors direct stimulation of undifferentiated "basal" cells. In arriving at this point of view I have considered the pertinent evidence obtainable from experimental and morphologic studies as well as that from the various clinical case records which have appeared in the literature.

POSSIBLE ROLE OF METAPLASIA (CLINICAL AND EXPERIMENTAL EVIDENCE)

Reports of squamous cell metaplasia of glandular gastric mucosa in both clinical and experimental studies have been sporadic, infrequent and not always easy to evaluate. Hermann,[2] for example, reported squamous cell metaplasia in the pyloric portion of the stomach in a woman 36 years of age who had suffered from two cicatricial stenoses in the distal portion of the stomach. The metaplasia was not associated with keratinization. There is no mention of definite intercellular bridges, and the report is not accompanied by photomicrographs.

From the Department of Pathology, Stanford University School of Medicine.

1. de Martel, T.; Oberling, C., and Pernet, J.: Bull. Assoc. franç. p. l'étude du cancer **19**:470, 1930.

2. Hermann, A.: Wien. klin. Wchnschr. **24**:168, 1911.

(It is of no little interest that this case has been alluded to by Martin and Pollosson [3] and Gauthier-Villars and Leger [4] as a case of epithelioma of the stomach. The case report, however, is confined to the question of metaplasia, and in reading Hermann's paper I am unabie to find any mention of tumor.)

The 21 cases of gastric neoplasm considered in this paper (tables 1, 2, and 3) fall into two large groups: One consisting of cases of pure squamous cell carcinoma and the other of cases of adenocarcinoma with a squamous cell component. Benign squamous cell metaplasia was consistently absent in these cases.

Experimentally, Fütterer [5] reported the production of unquestionable squamous cell metaplasia in rabbits. He reviewed the literature on squamous cell metaplasia in the stomach and could find only one example recorded, a case reported by Borst.[6] Fütterer demonstrated metaplasia of glandular to squamous epithelium in 5 of 94 rabbits to which he had given hypodermic injections of pyrogallic acid in order to delay the healing of incisional wounds of the stomach. His papers are accompanied by excellent photomicrographs. Attempts by other workers, however, to produce squamous cell metaplasia in the glandular gastric mucosa of lower animals have been as a whole unsuccessful. Most of the experimental studies have been confined to rats and mice. It is well to remember that the rodent stomach is not strictly comparable to the human. It consists of two chambers: (*a*) a forestomach comprising two thirds of the entire stomach and lined by squamous epithelium continuous with the esophagus, and (*b*) a glandular stomach separated from the forestomach by a slight elevation, the limiting ridge. These two chambers are lined by unrelated types of epithelium—squamous, nonsecreting epithelium in the forestomach, and glandular, secretory epithelium in the glandular chamber. Thus, their respective linings are capable of giving rise to two entirely different types of carcinoma. It is also well to remember that the term "experimental gastric cancer" in the literature almost always refers to squamous cell carcinoma of the forestomach unless a specific statement to the contrary is made. Vitamin A deficiency in rats and mice does not produce squamous cell metaplasia of the glandular mucosa; it produces atrophy of the epithelium.[7] As a result of a certain degree of malnutrition, or possibly as a result of certain dietary deficiencies whose exact nature is still uncertain, ulcerative and reversible proliferative lesions (papillary growths) develop in the forestomach of the white rat.[8] Brunschwig and Rasmussen in this same work show that only ulcerative lesions occurred in the glandular portion and that in none of their animals did squamous cell metaplasia of the glandular mucosa occur. It seems evident from experimental studies that the gandular mucosa is highly resistant to the effects of deficiencies as well as to the action of most carcinogenic agents. The dietary studies made in rats by Morris and Lippincott [9] are worthy of note in regard to proliferative and ulcerative gastric lesions which also occur in the absence of metaplasia. In rats on a fasting regimen with inanition ulcerating lesions develop in the glandular portion. Metaplasia is absent. Similarly, Howes and Vivier [10] produced proliferative lesions of the glandular chamber of the stomach in rats with deficient diets. None was associated with either cancerous

3. Martin, J. F., and Pollosson, E.: J. de méd. de Lyon **17**:553, 1936.
4. Gauthier-Villars, P., and Leger, L.: Ann. d'anat. path. **16**:1065, 1940.
5. Fütterer, G.: Ergebn. d. allg. Path. u. path. Anat. **9**:706, 1903; J. A. M. A. **43**:1129, 1904.
6. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, vol. 2, pp. 645-665.
7. Wolbach, S. B., and Howe, P. R.: J. Exper. Med. **42**:753, 1925.
8. Brunschwig, A., and Rasmussen, R. A.: Cancer Research **1**:371, 1941.
9. Morris, H. P., and Lippincott, S. W.: J. Nat. Cancer Inst. **2**:459, 1942.
10. Howes, E. L., and Vivier, P., Jr.: Am. J. Path. **12**:689, 1936.

change or squamous cell metaplasia. The lesions in the forestomach, consisting of hyperplasia, hyperkeratinization and ulceration of the squamous epithelium, could be prevented by the addition of whole yeast to the diet. They found that vitamin-free casein and vitamin A in various forms were of no protective value. According to Klein and Palmer,[11] in an extensive and critical review (1940), the experimental production of gastric adenocarcinoma in mice or rats is questionable. Since this critique, however, Stewart [12] has reported successes in the production of adenocarcinoma in the pyloric portion of the stomach of mice (strains C3H and I) by injection of methylcholanthrene (in some instances, dissolved in liquid petrolatum; in others, dissolved in horse serum) directly into the wall of the stomach. This constitutes the first authentic success of such an endeavor. In some of his mice (strains C3H and C57 black) adenoacanthoma was also observed.

(By injecting methylcholanthrene with serum as a vehicle into 47 C3H mice, the following results were obtained: adenoma in 7, adenocarcinoma in 6, adenoacanthoma in 6, adenocarcinoma and sarcoma mixed in 12, adenoacanthoma and sarcoma mixed in 2, sarcoma in 3, squamous papilloma in 9, squamous carcinoma in 2. This is the only strain in which mixed adenoacanthoma and sarcoma was produced. Adenoacanthoma developed in 1 mouse of the C57 black strain when methylcholanthrene was injected with oil as a vehicle. The authors produced adenoacanthoma of the stomach in a total of 8 mice. In 4 it involved both the forestomach and the pyloric chamber. In the other 4 mice it was confined to the pyloric chamber. One of the tumors produced hepatic metastases, also adenoacanthomatous in structure.)

CLINICAL REPORTS OF HETEROLOGOUS ADENOACANTHOMA

In man, heterologous squamous cell carcinoma and adenoacanthoma occur under the following three circumstances: (1) in organs where there are contiguous squamous cell and glandular surfaces (bronchus, rectum, uterus and region of the gastric cardia); (2) in organs frequently the site of squamous cell metaplasia (gallbladder and pancreas), and (3) in organs possessing glandular mucosa not contiguous with squamous epithelium and not known to manifest squamous cell metaplasia (pyloric end of stomach, cecum, colon). In this third group one should note specifically in addition to the pyloric site giving rise to adenoacanthoma the following sites of primary origin of similar tumors: ileocecal valve (Schmidtmann, "cancroid" [13]); cecum (Herxheimer, "adenocancroid" [14]; Humiston and Piette, "cholesteatoma" [15]; Tisenhausen, "heterologous cancroid" [16]); large intestine (Plenge [17]); ascending colon (Rabson, "adeno–squamous cell carcinoma" [18]); and sigmoid colon (Probst, "adenocancroid" [19]). In regard to the latter group of tumors it is to be reiterated that squamous cell components of the tumors developed in structures that were not contiguous with epidermoid mucosa and that were not the site either of squamous cell metaplasia or of the occurrence of heteroplastic

11. Klein, A. J., and Palmer, W. L.: Arch. Path. **29**:814, 1940; J. Nat. Cancer Inst. **1**:559, 1941.
12. Stewart, H. L., and Lorenz, E.: J. Nat. Cancer Inst. **2**:193, 1941; **3**:175, 1942.
13. Schmidtmann, M.: Virchows Arch. f. path. Anat. **226**:100, 1919.
14. Herxheimer, G.: Beitr. z. path. Anat. u. z. allg. Path. **41**:348, 1907.
15. Humiston, C. E., and Piette, E. C.: J. A. M. A. **84**:874, 1925.
16. Tisenhausen, M.: Ztschr. f. Krebsforsch. **14**:176, 1914.
17. Plenge, C.: Virchows Arch. f. path. Anat. **264**:370, 1927.
18. Rabson, S. M.: Arch. Path. **21**:308, 1936.
19. Probst, O.: Zur Kasuistik heterologer Darmkarzinome. Ein Adenocancroid des Colon sigmoideum, Thesis, Würzburg, F. Standenraus, 1909.

squamous epithelium. Again, as with the experimentally induced adenoacanthoma, it seems apparent that antecedent or concurrent squamous cell metaplasia is not a necessary factor in their evolution. The rarity of these tumors suggests further that the mechanism which sets in motion such polymorphous proliferation is extremely delicate and not easily invoked. In man heterologous adenoacanthoma is rare. Takagi [20] quoted Nochimouski, who found only 59 cases of "adenocancroid" of the various organs (the stomach being involved in only 5 of these). It is quite probable that such tumors are more common, however, than is indicated by this figure.

ADENOACANTHOMA AND HETEROLOGOUS SQUAMOUS CELL CARCINOMA OF THE STOMACH (WITH REVIEW OF CASES REPORTED TO DATE)

In this paper interest is centered chiefly in adenoacanthoma of the pyloric end of the stomach. The cases of squamous cell–containing carcinoma of the stomach can be divided arbitrarily in three ways: first, according to cellular structure (pure epidermoid carcinoma as contrasted with adenoacanthoma); second, according to the organ or tissue of origin (stomach, or esophagus or pancreas by extension, or distant primary tumor by metastasis), and third, according to the site of origin within the stomach (region of cardia, fundus, pyloric region).

TABLE 1.—*Adenoacanthoma of the Pyloric End of the Stomach*

Case	Author	Sex	Age	Type of Metastases	Comment
1	Rolleston and Trevor [25]	F	39	No histologic description	Predominantly adenocarcinoma
2	Lubarsch [26]	?	?	Mixed	Predominantly adenocarcinoma
3	Herxheimer [14]	?	?	None	Predominantly adenocarcinoma
4	Oberling and Wolf [22]	F	67	Adenocarcinoma	Predominantly adenocarcinoma
5	Boedeker [27]	F	35	(None ? not stated)	Predominantly adenocarcinoma
6	Boedeker [27]	F	65	(None ? not stated)	Equal admixture
7	Pasternack [21]	M	48	Adenocarcinoma	Predominantly squamous cell carcinoma
8	Wood	M	51	Mixed	Equal admixture
9	Wood	M	37	Mixed	Equal admixture

Mixed heterologous squamous cell–glandular carcinoma appears in the literature under a number of names—"adenoacanthoma" (Pasternack [21]), "adenocancroid" (Herxheimer [14]), "malpighian epithelioma" (Gauthier-Villars and Leger [4]), "polymorphous epithelioma" (Oberling and Wolf [22]) and "adenosquamous carcinoma" (Rabson [18]). With such a multiplicity of terms a certain amount of confusion has occurred. With no particular preference, I have chosen the term "adenoacanthoma."

The cases of squamous cell–containing carcinoma of the stomach which have been reported in the literature are reviewed by tabulation in four tables accompanying this article.

The cases of Pollack [23] and Duschl [24] have not been included among the cases of adenoacanthoma of the pyloric end of he stomach in table 1. In Pollack's case an epidermoid component was found in the pulmonary metastases, but none was demonstrated in the primary pyloric adenocarcinoma. Even though a more careful

20. Takagi, C.: Gann **31**:173, 1937.

21. Pasternack, J. G.: Am. J. Path. **11**:541, 1935.

22. Oberling, C., and Wolf, M.: Bull. Assoc. franç. p. l'étude du cancer **16**:68, 1927.

23. Pollack, K.: Beiträge zur Metaplasiefrage, in Arbeiten aus der pathologisch-anatomischen Abteilung, des königlichen hygienischen Instituts zu Posen, Wiesbaden, J. F. Bergmann, 1901, p. 154; cited by Rabson.[18]

24. Duschl, L.: Zentralbl. f. allg. Path. u. path. Anat. **33**:427, 1933.

search might have revealed squamous cell elements, the case strictly is not one of adenoacanthoma. Duschl's case is presented as a "Basalzellenkrebs des Magens (basal cell carcinoma of the stomach)," does not have a concise description and is not accompanied by photomicrographs.

More detailed information concerning the cases in table 1 is given in the following sentences. In the case reported by Rolleston and Trevor [25] the wall from within the pylorus for a distance of 3 inches (7.6 cm.) was thickened by a cancerous growth, which had ulcerated and perforated. The fundus and the cardia were free from cancer. (The left ovary had been removed 18 years previously.) Sections from the posterior wall showed adenoacanthoma in contrast with pure adenocarcinoma in the anterior wall. This tumor is described by the authors as a "columnar-celled carcinoma of the stomach showing squamous-celled metaplasia." Lubarsch [26] reported a pyloric adenocarcinoma in which there was one area of squamous cell carcinoma with intercellular bridges and epithelial fibrillation. In the metastases of the regional lymph nodes adenocarcinoma as well as squamous cell carcinoma was found. Herxheimer [14] reported a "fist-sized" annular tumor of the pylorus with miliary nodules on the serosa and two swollen lymph nodes behind the pylorus. The portion of the lesser curvature between the cardia and the tumor was completely free of tumor. Sections showed that even though the greater part of the tumor formed the picture of adenocarcinoma, there were areas of squamous cell carcinoma with prickle cells, stratification and keratinization. Oberling and Wolf [22] reported a case of pyloric tumor in which all the abdominal viscera were involved in a single mass, which was partly viscid. Numerous "viscid" metastases occurred in the liver and the peritoneum. One was found in the spleen. Microscopically, the tumor was "polymorphous carcinoma," composed chiefly of columnar cell adenocarcinoma with isolated islands of squamous cell carcinoma present. No transitions were seen between the columnar and the squamous cells. In Boedeker's [27] first case the tumor was situated on the anterior wall of the stomach just above the pylorus. It was the size of a "small fist" and polyp-like, and presented a cauliflower-like, ulcerated surface. It extended through the wall to the serosa but was not adherent to the neighboring organs. Microscopically, most areas consisted of adenocarcinoma, with a few foci manifesting a typical squamous cell component. Also present in this case was a small tumor of the ascending colon, interpreted as a second primary tumor and revealing the structure of adenocarcinoma. The second case was one in which a surgical specimen was obtained as the result of a Billroth I gastric resection. Situated just above the pylorus on the lesser curvature was a "small apple-sized" tumor with rather sharp borders which extended onto the posterior wall of the stomach. It consisted histologically of an equal admixture of adenocarcinoma and squamous cell carcinoma. Pasternack [21] reported a tumor of the pyloric wall which measured 9 by 6 by 4 cm.; it was not adherent to adjacent organs. This tumor was surgically removed, after which the patient lived four months. It was predominantly epidermoid and confined to the pyloric area of the stomach. At autopsy the esophagus and cardia were normal. The tumor in the vicinity of the gastric resection was predominantly adenocarcinoma, whereas the omentum, the lymph nodes and the pancreas were infiltrated only by adenocarcinoma.

25. Rolleston, H. D., and Trevor, R. S.: J. Path. & Bact. **10**:418, 1905.
26. Lubarsch, O.: Verhandl. d. deutsch. path. Gesellsch. **10**:198, 1906.
27. Boedecker, F.: Ztschr. f. Krebsforsch. **24**:406, 1926-1927.

The case reported by Martin and Pollosson [3] concerns a surgical specimen from a man who died postoperatively, in whose case permission for an autopsy was not obtained. It seems quite clear from their report, however, that the tumor was a primary gastric neoplasm and that it arose on the lesser curvature at some distance from the cardia. It was a large, centrally ulcerated tumor which had completely infiltrated the wall of the stomach and extended through to the serosa. There is no mention of metastases in the report. Histologically, the tumor was predominantly adenocarcinoma with typical squamous cell epithelioma in the central, more superficial portion. This component seemed to be bounded on all sides by adenocarcinoma. There was relative independence of the two types of carcinoma, neither component being admixed with the other and neither showing a transition to the other type. The adenoacanthoma in Takagi's case [20] was massive, the stomach wall being infiltrated from the cardia to the pylorus with a mucoid mass measuring up to 3 cm. in thickness. Associated with it in the epigastrium were several "head-sized" tumor masses, matting together the stomach, the greater omentum and the spleen. Histologically, even though the tumor was predominantly mucoid carcinoma, there were, scattered throughout, small nests of pavement epithelial cells with intercellular bridges but no definite keratin formation. Scheffler and Falk [28] reported 3 cases of epidermoid gastric carcinoma which they collected in Chicago. One of these falls into the classification of the cases

TABLE 2.—*Adenoacanthoma of the Stomach (Not Limited to the Pyloric Area)*

Case	Author	Sex	Age	Type of Metastases	Comment
1	Martin and Pollosson [3]	F	64	No data	"Voluminous" tumor
2	Takagi [20]	M	33	Mixed	Massive tumor
3	Scheffler and Falk [28]	M	74	Mixed	Adenocarcinoma component (photomicrographs)

listed in table 2 (a second in table 3 and the third in table 4). The tumor originated on the posterior wall of the stomach along the lesser curvature and was situated 7 cm. from the cardia. The tumor presented an ulcer 1.5 cm. in width, with indurated edges. The esophagus was normal. Although the description is not clear, it seems evident from the photomicrograph that the tumor is adenoacanthoma. The squamous cell component predominates.

In Roerig's case [29] (table 3) there was situated on the lesser curvature an ulcer the size of a "5 mark piece" with rounded edges and a necrotic, disintegrating center. The cardia was free, and its wall showed no infiltration. Microscopically, the tumor presented typical bulblike nests of squamous epithelial tumor cells with central keratinization. Eppinger [30] reported a tumor in the fundus of the stomach which had broken through into the transverse colon, had infiltrated the spleen and had exposed the caudal portion of the pancreas. Microscopically, the tumor consisted of pure squamous cell carcinoma. The author excluded the possibility of a metastasis or an "overlapping" from the cardia of the esophagus. Calderara [31] reported a gastric tumor, the macroscopic appearance of which was not unusual but which microscopically was squamous cell carcinoma. Calderara expressed the belief that only after the formation of the neoplasm did alteration to squamous

28. Scheffler, M. M., and Falk, A. B.: Am. J. Cancer **38**:359, 1940.
29. Roerig, R.: Primäres Cancroid des Magens, Inaug. Dissert., Thesis, Würzburg, P. Scheiner, 1895.
30. Eppinger: Prag. med. Wchnschr. **20**:218, 1895.
31. Calderara, A.: Virchows Arch. f. path. Anat. **200**:181, 1910.

epithelium take place. Histologically, there were massed strands of cells, which peripherally were multilayered and cylindric, with small oval nuclei. An intermediate zone was formed of polymorphic cells. Centrally, the cells were flatter, with homogeneous cytoplasm, and formed true "epithelial pearls." De Martel, Oberling and Pernet [1] presented a case in which a massive tumor of the pyloric region was surgically resected. The gastric lymph nodes were extensively invaded by the tumor cells. Apparently, however, no visceral metastases existed. (No note was made as to the ultimate outcome, although it is stated that the "cure was effected without incident.") The tumor was the size of an adult's palm and situated on the posterior wall of the pyloric antrum, extending toward the lesser curvature. Centrally there was an ulcerated area, 4 by 5 cm. Histologically, the tumor was pure squamous cell carcinoma. Even though no true keratinization was seen, the cells frequently formed parakeratotic pearls. "From the point of view of structure, it is malpighian epithelioma of the imperfect spinocellular type, resembling closely epithelioma of the tongue or of the cervix." The tumor reported

TABLE 3.—*Pure Squamous Cell Carcinoma of the Stomach*

Case	Author	Sex	Age	Comment
1	Roerig [29]	?	?	Lesser curvature. History and autopsy protocol not deemed necessary. No data other than those pertaining to specimen
2	Eppinger [30]	M	?	Fundus. Gastrocolic fistula with local extension
3	Borst [6]	?	?	No data. Illustration of cornifying gastric carcinoma, referred to in text but without data
4	Calderara [31]	F	54	Pylorus
5	de Martel, Oberling and Pernet [1]	M	41	Pylorus. (Large carcinomatous ulcer occupying whole region of pylorus and extending upward along lesser curvature. Lymph node but no visceral metastases. Surgical specimen)
6	Penna de Azevedo and Villela [32]	M	57	Lesser curvature. Attached to pancreas
7	Weil, G. H.: Strassbourg méd. **96**: 45, 1936	M	47	Stenosing pyloric tumor, thickest on anterior wall; old antecedent ulcer (?)
8	Gauthier-Villars and Leger [4]	M	68	Limited to pylorus; size of orange
9	Scheffler and Falk [28]	M	49	4.5 cm. from cardia

by Penna de Azevedo and Villela [32] was situated on the lesser curvature, appeared as a crateriform ulcer 3.5 cm. in diameter and was adherent to the pancreas. Neither the esophagus nor the cardia was involved. Metastases were numerous, and in all places the tumor maintained the epidermoid structure of the primary lesion. Gauthier-Villars and Leger [4] report with meager description a neoplasm the size of an orange involving the pyloric portion of the stomach. Sections of the surgical specimen showed typical squamous cell carcinoma with whorls of squamous epithelial cells, some of which showed centrally keratinized plugs. The authors felt that the possibility that this tumor was a metastasis from a primary tumor elsewhere had been definitely excluded. There is no follow-up report as to the subsequent course of the patient. The case of pure squamous cell carcinoma which Scheffler and Falk [28] reported was described from the records of the Cook County Hospital in Chicago.

. . . Autopsy revealed a large oval defect, 8 x 5 cm. in diameter, along the greater curvature of the stomach, 4.5 cm. from the cardiac end, opening into a large cavity, the lateral

32. Penna de Azevedo, A., and Villela, E., cited by Gauthier-Villars and Leger [4] and Scheffler and Falk.[28]

wall of which was formed by the spleen. There was a defect in the wall of the colon at the splenic flexure communicating with the cavity. Histologically, the edge of the ulcer in the stomach revealed a squamous-cell carcinoma.

Photomicrographs reveal typical squamous cell carcinoma.

In Kaufmann's case [33] a large tumor was situated on the posterior gastric wall. It was a keratinizing squamous cell carcinoma, gradually disappearing at the esophageal border, with infiltrations progressing to the liver. In the case reported by Rolleston and Higgs [34] there were two epidermoid tumors, one situated in the lower part of the esophagus and the other in the fundus. The latter was large and irregularly circular; it covered an area the diameter of which varied from 3 to 4 cm. The tumor was situated slightly to the left of the esophageal opening, and infiltrated the anterior wall of the stomach, which was adherent to the inferior surface of the left lobe of the liver. The latter was infiltrated by direct extension of the growth, and there was an associated large cavity formed by pyogenic action. There also were secondary metastases in the liver. The tumor at the lower end of the esophagus was separated from the fundic mass by an intact zone of mucosa approximately 3 cm. in length. The esophageal mass was oval and somewhat polypoid, and had its axis in the midanterior line. It covered an area

TABLE 4.—*Squamous Cell Carcinoma of the Stomach (Primary Site Uncertain)*

Case	Author	Sex	Age	Probable Site of Origin	Comment
1	Kaufmann [33].....	M	42	Esophagus	Large tumor in stomach near cardia, diminished, however, toward esophagus
2	Rolleston and Higgs [34]...	M	40	Esophagus	Two epidermoid tumors, one in esophagus, other in stomach
3	Vinson and Broders [35]....	F	46	Esophagus	Specimen from gastrostomy showing lesion at esophageal cardia
4	Cabot case no. 19442 [36]...	M	64	Esophagus	Large tumor at cardia; too large for primary site to be determined with accuracy
5	Scheffler and Falk [26].....	M	63	Esophagus	At cardia of stomach

approximately 5 by 2 cm. in size. Microscopically, the two tumors were of similar structure, consisting of squamous epithelial tumor cells associated with much keratinization and formation of cell nests. Both tumors appeared to be chiefly in the submucosal layers, and neither showed definite signs of having arisen from their respective mucous membranes. Vinson and Broders [35] reported a case in which there had been symptoms of esophageal obstruction for seventeen years. When obstruction became suddenly complete, gastrostomy was performed. Through the gastrostomy opening a small bronchoscope was introduced into the stomach and a piece of tissue removed from an ulcerating lesion involving the "upper half" of the stomach. Microscopic sections showed the tumor to be squamous cell carcinoma, grade 3. A very large cancer was reported [36] as Cabot case 19442. It was situated chiefly in the stomach rather than in the esophagus. It was so high in the stomach that it completely surrounded the cardia. In one or two areas it had grown along beneath the submucosa beyond the sphincter, so that there was a slight amount of tumor actually above the cardia. Dr. Tracy

33. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Ärzte, Berlin, W. de Gruyter & Co., 1931, p. 553.

34. Rolleston, H. D., and Higgs, F. W.: Brit. M. J. **1**:1293, 1907.

35. Vinson, P. P., and Broders, A. C.: J. Lab. & Clin. Med. **11**:258, 1925.

36. A Case of Esophageal Obstruction, Cabot Case 19442, New England J. Med. **209**:918 1933.

Mallory felt "distinctly uncertain" as to its primary site of origin. He commented that "the gross appearance certainly suggested stomach, but the histology, which shows an epidermoid carcinoma, is more in favor of an esophageal origin." The tumor reported by Scheffler and Falk [28] (from the Cook County Hospital records) was a large friable tumor involving the entire cardiac end of the stomach and extending up into the esophagus for a distance of 4 cm. Histologically, the tumor was poorly differentiated squamous cell carcinoma of the cardioesophageal junction.

Several tumors, such as the one reported as primary epidermoid carcinoma of the stomach by Vinson and Broders [35] and that by Kaufmann,[38] were most probably bulky extensions from small primary tumors near the cardia in the esophagus, which had advanced by submucosal lymphatic permeation. Squamous cell carcinoma of the stomach also arises from the small islands of heterotopic pavement epithelium which are occasionally found between the cardiac glands of the stomach. The development of squamous cell carcinoma elsewhere in the stomach, however, seems to be on an entirely different basis. Massive diffuse adenoacanthoma involving all the stomach, as in the case reported by Takagi,[20] in all probability arises on the same basis of stimulation as does adenoacanthoma of the pyloric portion.

REPORT OF TWO ADDITIONAL CASES OF ADENOACANTHOMA OF THE PYLORIC REGION OF THE STOMACH

Because of the anatomic detachment of the pyloric area from squamous epithelium, adenoacanthoma in this site assumes critical interest. Because of this and because of its rarity 2 cases of adenoacanthoma of the pyloric end of the stomach are reported. These together with those previously reported bring to 9 the total of cases in the literature as of this date.

CASE 1.—A 51 year old Puerto Rican cook was admitted to the medical service of Stanford University Hospitals Aug. 15, 1937, complaining that he had suffered from pain in the left side for eight months. The family history was without bearing on this complaint. Previous admissions into hospitals had resulted in diagnoses of schistosomiasis, latent syphilis, osteoarthritis and inguinal hernias. Following a recurrence of right inguinal hernia and a herniorrhaphy in April 1937, he failed to gain in strength. At this time he first noted that the pain in the left flank was intensified by ingestion of food. Associated with the pain there was aching in the interscapular region, especially to the left of the spinal column, radiating at times to the precordium. For two months prior to examination he had nausea after eating and induced emesis, with production of coffee ground material on several occasions. The stools were black during this time. There had been periodic bouts of dyspnea on exertion and edema about the ankles.

The patient was a thin, ill middle-aged man. Except for tenderness in the left upper quadrant of the abdomen and in the interscapular region, the results of examination were not remarkable.

The erythrocyte count was 4,100,000; the hemoglobin content, 62 per cent (Sahli); the white cell count, 6,000, with normal differential percentages. The urine was normal. There was no free acid in the gastric secretion even after histamine was given as a stimulus; the highest ten minute volume was 2.2 cc.

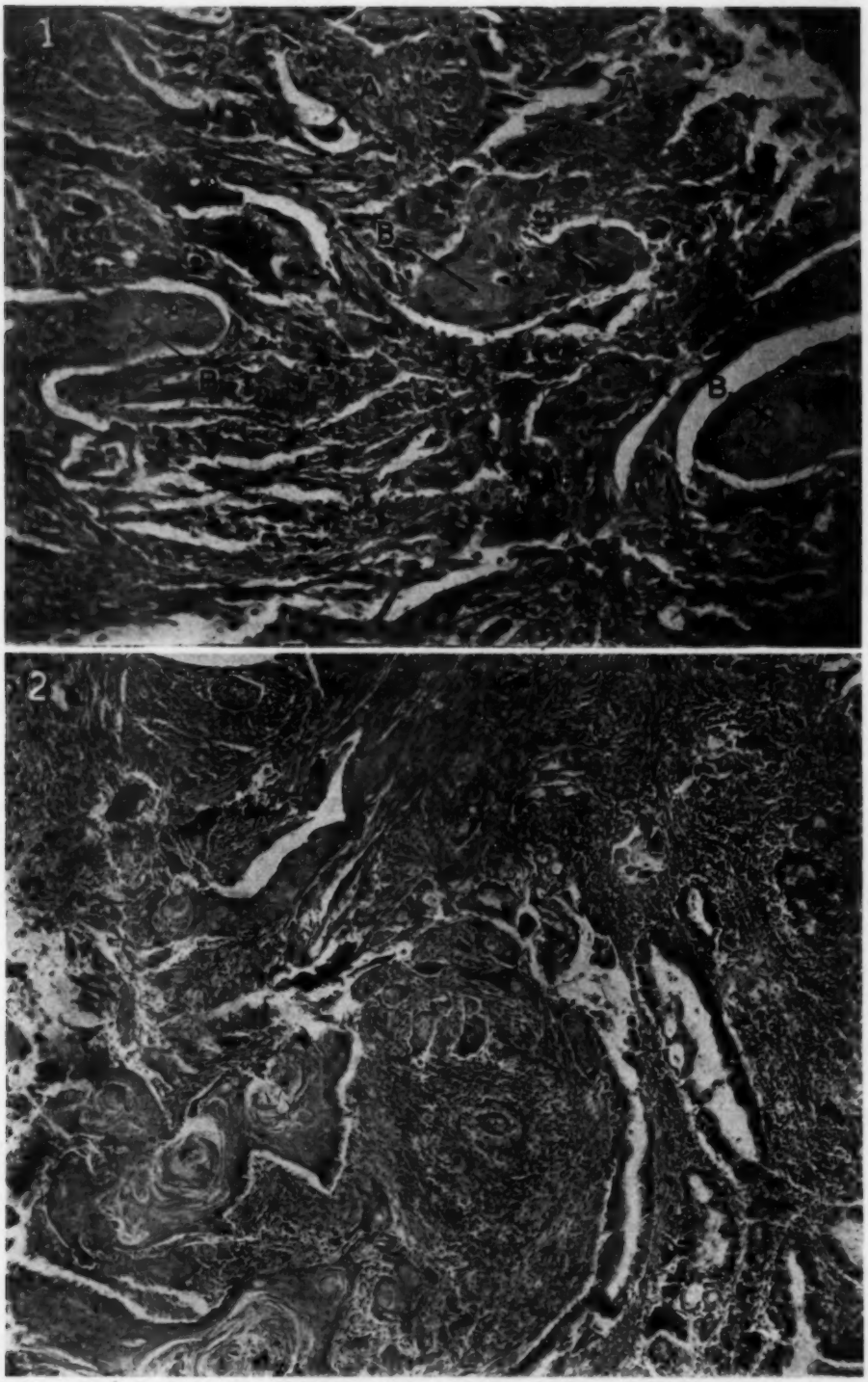
Roentgen examination of the stomach revealed a constant filling defect on the lesser curvature just proximal to the pylorus.

When viewed through the gastroscope, the lesion presented two punched-out areas from which blood was oozing and about which there were high stiff folds of mucosa.

The tumor was demonstrated at operation and a large mass of firm, nodular lymph nodes was seen along the spinal column in the region of the diaphragmatic crura; no metastases were seen in the liver. Because of the high degree of gastric retention demonstrated previously, partial resection and gastroenterostomy were done.

After a normal postoperative course, intractable pain developed. He was made comfortable until he died in March 1938. There was no necropsy.

Gross Specimen.—The pathologic tissue consisted of a portion of stomach and pyloric wall, with small tags of moderately fatty mesentery and omentum attached. The specimen when fixed in a 4 per cent solution of formaldehyde weighed 91 Gm. It was 5 cm. in length, 8 cm.



1 (case 1) shows glandular structures lined by low cuboidal epithelial tumor cells (*A*). The squamous epithelial tumor cells are arranged in whorls, some of which show a slight attempt at beginning keratinization (*B*). × 200.

2 (case 2) shows adenoacanthoma in the pyloric region of the stomach consisting of well differentiated squamous epithelial tumor cells with keratinization, and rather well formed glandular structures. × 200.

in width, 17 cm. in circumference and up to 2 cm. in thickness. Posteriorly, near the pylorus and midway between the greater and lesser curvatures was a cluster of subserosal nodules measuring 1.5 cm. in diameter. They were firm and white. The serosal blood vessels were not injected. When the stomach was opened along the greater curvature, the pylorus was seen to be thickened and hard. The wall of the stomach otherwise appeared slightly edematous. On the lesser curvature was a firm mass, 5 by 7 by 1 cm. In its midportion it presented a shallow ulcerated area, 2 by 1 cm. The ulcer was 0.3 cm. in greatest depth. The floor of the ulcer was continuous with the rosette of nodules described as situated in the subserosa. On cut section the tumor was found to be noncircumscribed, hard, white and glistening, and to invade the full thickness of the gastric wall. Three firm lymph nodes along the greater curvature measured up to 1.5 by 1 cm. All contained white firm areas.

Histologic Examination.—Sections showed a sudden transition from a normal, though slightly heaped up, gastric mucosa to widely proliferating epithelial tumor cells which readily invaded the entire wall of the stomach. In the light connective tissue stroma there was fair glandular formation, but as the growth approached the serosa, sheets of huge squamous type cells with large vesicular nuclei were present and were seen to permeate lymphatic channels. Some of the squamous cells were arranged in whorls and showed a slight attempt at central keratinization (fig., *1*). In some regions mitotic figures were numerous. Sections of the lymph nodes showed them to be replaced by tumor, some of which was squamous in type and some of which was glandular.

Dr. George Armanini and Dr. E. K. Blasdel, of the Tulare County Hospital, gave me the morphologic material of an interesting case, described in the following section.

CASE 2.—A 37 year old white American laborer was admitted to the Tulare County Hospital in November 1939, complaining that he had experienced epigastric distress for three years. The fluoroscope and roentgen films made after barium sulfate meals showed a persistent ulcer defect at the pylorus. Previous admissions to the hospital had resulted in a diagnosis of peptic ulcer with increasing pyloric obstruction. Six months previously there had been demonstrated retention of only 10 per cent after six hours in contrast to retention of 70 per cent at the time of this examination. For the preceding three years the patient had been on a strict medical regimen, but his symptoms had gradually become worse.

Operation disclosed a firm mass involving the pyloric portion of the stomach. Lymph nodes along the lesser curvature were enlarged and hard. Because of the high degree of retention, the distal half of the stomach was resected and gastrojejunostomy performed.

Gross Specimen.—The resected distal portion of the stomach measured 8 cm. in length. Attached to it was a narrow proximal segment of duodenum, which had been excised just distal to the pylorus. Beginning immediately above the pylorus on the lesser curvature was a rather shallow ulcer 4 cm. in length, with hard edges. The adjacent mucosa was thrown into prominent rugae. The base of the ulcer was composed of hard, noncircumscribed tumor which completely infiltrated the wall and measured up to 2.3 cm. in thickness. Along the lesser curvature were four enlarged, hard lymph nodes, the largest measuring 1.5 cm. in width. Grossly, the nodes were infiltrated by firm white tumor.

Histologic Examination.—The mucosa was interrupted by tumor, which extensively invaded the submucosa and the muscularis. The tumor was of pleomorphic structure. In some places it consisted of large, atypical glands, and elsewhere it contained large sheets and irregular whorls of squamous epithelial tumor cells. In the former areas the glands were lined by columnar epithelial tumor cells. In the epidermoid areas the squamous epithelial tumor cells were arranged in whorls, which showed a moderate attempt at central keratinization. Mitotic figures were infrequent. Some whorls showed definite "pearl formation" (fig., *2*). The lymph nodes were extensively infiltrated by tumor which presented the structure of both adenocarcinoma and acanthomatous carcinoma.

After an uneventful postoperative course, the patient was readmitted to the hospital July 16, 1941, a year and a half later. Three months prior to this entry epigastric pain had recurred, anorexia had developed, and he had lost considerable weight.

Examination revealed an emaciated man. There was palpable in the epigastric region an irregular hard mass. The edge of the liver could be felt beneath the costal margin and was not only hard but irregular. His course was progressively downhill until he died, Aug. 21, 1941. An autopsy was made a few hours later.

Necropsy.—The body was that of an emaciated, slightly icteric man, who appeared to be about 40 years of age. A well healed midline surgical scar was present in the epigastrium. When the peritoneal cavity was opened, the intestines were found matted together by

numerous adhesions. In the epigastrium they were adherent to a firm mass which originated in the region of the duodenal stump and which was continuous with large masses about the celiac axis. The gastrojejunostomy opening was patent and free. No residual tumor was found in the stomach.

The liver was normal in size. The posterior surface of the left lobe was adherent to the tumor over a 3 cm. area. Here the liver was invaded by direct continuity. A smaller isolated nodule 0.4 cm. in width was situated just beneath Glisson's capsule in the main lobe, anteriorly.

The gallbladder was slightly distended and contained approximately 70 cc. of thick bile. In its serosa was a milky-white area of thickening and induration 0.5 by 1.2 cm. in size. No stones were contained within the gallbladder. Even though large firm nodes surrounded the common bile duct, the extrabiliary passages were patent and their lining mucosa intact.

COMMENT

In each of the 2 cases just reported the tumor produced not only definite glandular structures lined by epithelial cells varying in form from cuboidal to columnar but also definite squamous epithelial tumor cells arranged so as to form solid cords and well defined whorls with central keratinization and so-called pearl formation. Each showed mixed components in the lymph node metastases, although the squamous component was not as distinct as it was in the primary tumor. In neither case could there be detected a transition between columnar and squamous cells. These components, however, were intimately admixed throughout. Case 1, with a clinical course of approximately one year, was in contrast with case 2 in which the course extended over a period of five years.

Metastasis of the epidermoid component occurred in only 1 of the 7 cases of pyloric adenoacanthoma which have been described in the literature (see table 1). In the case reported by Lubarsch [26] metastases of squamous cell carcinoma in distant lymph nodes prompted further study of the primary adenocarcinoma in the pyloric end of the stomach, with the discovery of a single area of squamous cell carcinoma. Pollack [23] reported a somewhat similar case but one in which epidermoid constituents were not found in the primary gastric adenocarcinoma. In his case typical squamous epithelial tumor with intercellular bridges and beginning keratinization was found in the pulmonary metastases. Herxheimer [14] in reviewing this case expressed the opinion that a more careful examination of the primary neoplasm would probably have revealed areas of squamous cell carcinoma.

The metastases in the 2 cases I have reported were in the regional lymph nodes and as regards the route of metastasis differ in no respect from metastases of the usual gastric carcinoma. There is no reason to suspect either of the tumors as representative of metastatic lesions. In this regard it is well to point out that the stomach is a rare site of metastasis from tumors of other organs. Of 1,000 cases of carcinoma in the Stanford autopsy statistics reported by Liljencrantz,[37] only 25 showed metastasis to the stomach.

Squamous cell metaplasia does not seem to be necessary to the evolution of adenoacanthoma. Support for this view is obtained from a review not only of clinical data but also of the experimental studies which have been made in lower animals.

The experimental production of adenoacanthoma in the pyloric chamber of the stomach of the mouse and the development of adenoacanthoma in the pyloric region of the human stomach are highly significant from the point of view of histogenesis in that the only explanation for the origin of the adeno-

37. Liljencrantz, E.: Cancer Handbook, Stanford University, Calif., Stanford University Press, 1939.

acanthoma would be that of stimulation of the glandular mucous membrane. It is also significant that this lesion is carcinomatous from the beginning and shows no evidence of antecedent or concurrent squamous cell metaplasia. The squamous cell component develops seemingly de novo. The exact nature of the process is beyond the scope of this paper. However, it does seem quite clear from both experimental and clinical observations that antecedent squamous cell metaplasia is not a necessity.

In a review of the various experimental studies already discussed it seems that adenoacanthoma develops as the result of direct stimulation of the gastric glandular mucosa by the "carcinogen." Once neoplasia is initiated, it may show varying degrees of "redifferentiation," as manifested by the presence of not only columnar but also keratin-producing squamous cells. The methylcholanthrene experiments of Stewart suggest that a carcinogenic mechanism, as yet not understood, may occur which by direct stimulation gives rise to "mixed" or heterologous neoplasms. The carcinogenic agent, whatever its ultimate nature may prove to be, most probably acts by directly stimulating undifferentiated basal cells (normally present in the mucosa) to proliferation along two distinct lines leading to squamous and glandular cells.

SUMMARY

Two cases of adenoacanthoma of the pyloric end of the stomach are reported. In both cases the metastases in lymph nodes contained squamous cell as well as glandular components.

A total of 19 cases of squamous cell carcinoma of the stomach reported in the literature have been reviewed. In addition to these there have been considered separately 5 cases which appeared similar but in which the neoplasm most probably had its origin in the esophagus and not in the stomach. Seven of the 19 cases were instances of adenoacanthoma limited to the region of the pylorus; 3 were instances of adenoacanthoma not limited to the pyloric region, and 9 were instances of pure epidermoid carcinoma.

Experimental studies have been reviewed referable to the production of squamous cell metaplasia in the glandular portion of the stomach and its relation, if any, to the development of adenoacanthoma. The reported experimental production of adenoacanthoma in mice indicates that preexisting squamous cell metaplasia need not be present.

Squamous cell metaplasia in the glandular portion of the stomach is rare, and its presence is not considered essential to the development of adenoacanthoma.

The necessity of heterotopic squamous cell tissue in the pyloric end of the stomach is considered unlikely and as a remote possibility.

Direct neoplastic stimulation of undifferentiated basal cells in the gastric mucosa is considered as the essential factor in the histogenesis of squamous cell tumors of the pyloric region of the stomach.

A NOTE ON THE SO-CALLED UNDIFFERENTIATED AND EMBRYONIC CELLS

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Rapid progress of experimental embryology during the late part of the nineteenth century had an important influence on pathology. Theories explaining origin and growth of tumors by relating them to persistent embryonic tissue were supported by the discovery of the peculiar properties and extensive formative potencies of embryonic cells. During the early part of the present century the foremost pathologists and embryologists discussed explanations of tumor formation on the basis of origin from undifferentiated embryonic cells present in the mature organism. In the following decades many terms and concepts of this era were taken over into the literature and often used without adequate consideration of their foundation in experimental embryology. An effort will be made in the following pages to point out what position these concepts should take in the light of modern developmental physiology. However, it is not the purpose of the present report to evaluate the relative merits of these theories of tumors as against others.

Undifferentiated cells are also discussed in another relation to the problems of tumors. In so-called immature cancer cells are found with a low degree of structural differentiation. Here, however, the final condition, and not necessarily that of the mother tissue, is referred to as undifferentiated.

Finally, normal histology has made use of the concept of undifferentiated cells in the adult organism. Particularly Maximow [1] described under this name certain connective tissue cells which are believed to have the potency (and perhaps the purpose) to differentiate into various other cell types, as the need may be.

The following discussion of these subjects was planned after numerous articles in the literature as well as conversations had convinced me that the customary presentation of the problems in question tends to mislead those who have no thorough and specialized knowledge of modern developmental physiology. On the other hand, neither embryologic nor physiologic textbooks present the physiologic basis of these problems in such a manner as to enable the reader to judge critically the concepts in question. After a brief discussion of the physiologic basis, the following subjects will be considered: (1) origin of tumors from embryonic cells, (2) undifferentiated cells of immature cancers and (3) undifferentiated cells in the normal adult organism.

THE GENERAL CHANGES OF CELLS DURING DEVELOPMENT

Students of developmental physiology believe that potencies are inherent in any cell strain from the beginning of its existence, either indefinitely or until they are irrevocably lost during ontogenesis. It follows that the fertilized egg cell is omnipotent, since its descendants develop into all tissues of the body. Experimental evidence has been furnished to the effect that after the first few cell divisions which initiate the development of an organism, the daughter cells or blas-

1. Maximow, A.: Klin. Wchnschr. **5**:2193, 1926; Arch. Path. **4**:557, 1927.

tomeres are still omnipotent in many animal species (Spemann [2]; Weiss [3]). Under normal circumstances each of these blastomeres would form only part of the variety of tissues and organs, but when isolated from the other blastomeres, it may form a complete embryo. This shows that the range of potencies may greatly exceed the requirements of normal development, and similar general results have been obtained by experiments on organ development in older embryos (Spemann [2]; Weiss [3]). Various circumstances which the scope of the present report does not include gradually determine just which one of the various types of development made possible by their potencies, the cells of the developing organism will undergo. This determination is invisible in itself and can be tested only experimentally, but it is followed sooner or later by structural differentiation in the chosen direction. In the course of this development the range of potencies may be reduced, but not necessarily to the extent that only those remain which are used in the differentiation actually occurring. It is highly questionable that a condition termed fixed determination by the early experimental embryologists actually occurs. According to the definition, it should be impossible to change this kind of determination by any means, and in that event the presence of latent potencies could be denied. More recent experimentation has revealed that morphologic determinations which were thought to be fixed may change under certain new conditions, such as those of regeneration [4] or of tissue culture.[5] Consequently, one must assume that lability of determination and presence of latent potencies are more common than the early experimental embryologists believed. In fact, Fischel [6] called attention to this possibility as early as 1902. Harrison [7] lately discussed the problem of determination and the shortcomings of its classic version. One further knows that latent developmental potencies and lability of determination and differentiation are not, as early investigators believed, peculiarities of embryonic cells. One has reason to suspect, and in some cases to assume, that normal and typical cells of the adult organism have extensive latent potencies (see later section), and one is not entitled to call them embryonic for that reason.

Much confusion has been caused by attempts to correlate structural differentiation with the range of latent potencies. It must be kept in mind that there can be no morphologic criteria of such potencies. Only the further course of normal or abnormal development can reveal potencies, and some of them may remain unknown and dormant until new experimental procedures are devised to activate them. A cell with a low degree of differentiation does not necessarily have a wider range of potencies than a highly differentiated one. It will soon be pointed out that cells have been called undifferentiated to indicate their pluripotentiality. This is just as incorrect as the statement that a cell cannot have latent potencies because it is highly differentiated. No morphologic terms and characteristics can serve to indicate the developmental potencies of cells.

EMBRYONIC CELLS AS TUMOR GERMS

The vast amount of literature which followed the publication of the classic embryonic theory of tumors has briefly been mentioned. A comprehensive

2. Spemann, H.: Embryonic Development and Induction, New Haven, Conn., Yale University Press, 1938.
3. Weiss, P.: Principles of Development, New York, Henry Holt & Company, Inc., 1939.
4. Schotté, O. E., and Hummel, K. P.: J. Exper. Zool. **80**:131, 1939.
5. Törö, E.: Anat. Anz. **72**:248, 1931.
6. Fischel, A.: Verhandl. d. deutsch. path. Gesellsch. **5**:255, 1902.
7. Harrison, R. G.: Am. Naturalist **67**:306, 1933.

review by Herxheimer [8] dates approximately from the end of this period. By that time many authors singled out one group of tumors as forming on the basis of embryonic developmental anomalies—e. g., teratoma. Following a suggestion by Schwalbe (quoted by Herxheimer [8]), these tumors were termed dysontogenic blastomas. Many writers have proposed to apply the embryonic theory only to that group, and this limited form is still recognized today. For a modern review of theories of tumors the reader is referred to Ewing.[9]

There can be no doubt of the correctness of the embryonic theory of tumors in many instances. In other cases, however, embryonic origin was assumed only on the basis that some developmental anomaly must have occurred, since the tumor tissue did not correspond with the normal tissues in the respective site. It was pointed out in a previous communication [10] that two kinds of abnormal developmental processes must be considered in such cases: aberrant germs, and abnormal differentiation of cells in loco. The former are originally part of a normally located primordium. They secondarily lose their normal relation to the rest of the primordium and are later found more or less separated and distant from their mother tissue. In contrast to this, abnormal differentiation in loco occurs if the cells have the necessary developmental potencies which would normally remain dormant. Persistence of normally degenerating organs or tissues might be added as a third possibility; it is an aberration in time rather than space. In some cases one may suspect the cause of such tissue malformations, and thus drive analysis one step further. Mathias [11] pointed out that dystopic tissues and tumors are often found in places where they normally occur in phylogenetic ancestors. He called the tumors originating from these atavistic tissues progonoblastomas. The mechanism of development of atavistic dystopia is the same as that of others, and conforms with one of the aforementioned possibilities.

Regeneration is an important factor in the eliciting of abnormal growth and differentiation. The highly active regenerating tissues are probably highly susceptible to abnormal stimulations, and not always sufficiently well controlled by the regulations maintaining the normal pattern of the organism. A good example is carcinoma originating from futile bile duct regenerates in the cirrhotic liver. These anomalies of regenerating tissues, being either outgrowths from normal tissues or abnormal differentiations, are also covered by the already cited possibilities of formation of tissue anomalies.

None of these processes is limited to embryonic life, and thus dysontogenic tumor formation does not necessarily imply an embryonic anomaly. The parts in question may have been perfectly normal at the end of embryonic life. One must remember that birth in no way changes the principles of development of an organism. In many instances one may be tempted to think of embryonic origin if the structure of a tumor suggests the presence of potencies normally not activated in the respective site. However, the possibility of a wide distribution of latent potencies after birth was emphasized in the foregoing pages, and one must consider the fact that normal adult tissues may have the potencies which the creators of the embryonic theory of tumors believed to be present only in early embryonic cells (Gruenwald. [12]). Even such tumors as teratoma may originate

8. Herxheimer, G., in Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1913, pt. 3, supp., p. 51.

9. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B Saunders Company, 1941.

10. Gruenwald, P.: J. Urol. **48**:244, 1942.

11. Mathias, E.: Virchows Arch. f. path. Anat. **236**:424, 1922.

12. Gruenwald, P.: Proc. Inst. Med. Chicago **13**:382, 1941.

long after birth, as was shown by the results when zinc salts were injected into the testis (Michalowsky [13]). If it should be true that the dermoid or the teratoma of the gonads originates from sex cells, it could not be ascribed to embryonic cells of the bearer, but perhaps to embryonic cells of the next generation, being a descendant of a germ cell.

Thus one may maintain the dysontogenic explanation for the origin of many tumors, but with the definite understanding that ontogeny as referred to by this term is not limited to the embryonic period of life. Therefore, the term "embryonic" should not be used indiscriminately and as a synonym of "developmental" unless there are good reasons to assume that the anomaly in question originated before birth.

UNDIFFERENTIATED CELLS IN IMMATURE CANCERS

Not much need be said about the interpretation of those cells of low differentiation which constitute the so-called immature and usually highly invasive cancers. All authors will accept at least the possibility that these cells are descendants of fully differentiated body cells. The low differentiation of the cancer cells would then be the result of a process of dedifferentiation during the development of the cancer. The possible causes and consequences of such dedifferentiation and its relation to abundant proliferation cannot be discussed here. The question of formative potencies of these cells is not yet answered; it may well turn out that the cells have, in spite of their low differentiation, limited potencies. With this possibility in mind, one should be careful to distinguish the cells of the tumors in question from other cells of low differentiation mentioned in this report. This can be done by the use of such terms as "dedifferentiated" or "anaplastic." For similar reasons one should not designate cancer cells as immature without considering whether this actually conveys the desired meaning; for not every cell of low differentiation is necessarily immature. Referring to the cells under consideration, Ewing [9] explains: "Anaplastic cells are not embryonal cells, but a new type which have lost their place in the organization."

UNDIFFERENTIATED CELLS IN THE NORMAL ADULT ORGANISM

It has commonly been assumed that the tissues of the normal adult organism consist of differentiated cells, and it was under this assumption that embryonic remnants of some kind were held responsible for abnormal growth which seemed to originate from cells of low differentiation. Most discussions of the state of differentiation of cells expressed or implied a relationship between differentiation and the range of formative potencies in the sense that progress of the former is firmly linked with regression of the latter. I have said that this is not necessarily the case. In the field of normal histology this problem was brought into the center of discussion when Maximow [1] described undifferentiated mesenchymal cells in the adult organism. (It must be made clear that the following discussion does not take issue with the excellent findings of Maximow. An effort will be made to interpret and formulate them in accordance with the physiologic principles already outlined, assuming that the findings themselves are correct.) One would expect an undifferentiated mesenchymal cell not to have differentiated beyond the condition of the mesenchymal cell proper which one finds in the early embryo. This may actually hold for Maximow's fixed undifferentiated mesenchymal cells which he found to be most abundant in the vicinity of small blood vessels. However, the name is given to these cells because they are

13. Michalowsky, I.: Centralbl. f. allg. Path. u. path. Anat. **38**:585, 1926.

found to be endowed with all potencies of the embryonic mesenchyme, in contrast to the other types of fixed connective tissue cells. The difficulties increase when it is pointed out that certain free cells, namely, lymphocytes and hemocytoblasts, are endowed with the same wide range of mesenchymal potencies, and the term "undifferentiated mesenchymal cells" is applied to them, too. It can hardly be conceived that two cell types as different from each other as lymphocytes and perivascular mesenchyme should both be undifferentiated mesenchymal cells. Their difference in structure and function alone shows that they are differentiated in divergent directions. This differentiation, however, excludes in no way the presence of complete mesenchymal potencies in both cell types.

Similar considerations apply to many other tissues, and progress of experimental histology is supplying an ever increasing number of examples of pluripotent differentiated cells in the adult organism. In none of these cases does the visible differentiation allow any conclusion as to the range of latent potencies; these can be detected only by tracing normal or abnormal development under natural or experimental conditions.

Pathologists should not attempt to find a convenient one word substitute for "undifferentiated cell." When they designate a cell as pluripotent (which most cells probably are), they have to amplify this term by a statement of the quality of the potencies involved. This may be inconvenient, but it will give correct and valuable information. Simplicity, on the other hand, is no sufficient reason for using misleading terms, particularly when fundamental concepts are involved. It is to be hoped that increased exploration of developmental potencies will lead to helpful improvements in terminology.

SUMMARY

"Undifferentiated" and "embryonic" cells as described in the literature of pathology and histology are discussed on the basis of modern developmental physiology. It is found that most of the concepts in question are based on the old idea that only undifferentiated or embryonic cells can be credited with possessing latent developmental potencies. It is known now that such potencies may be present in differentiated cells of the adult organism as well, and that their presence is not correlated with morphologic characteristics. Much confusion has been created by the use of morphologic terms to indicate the state of potencies in a cell or tissue. This procedure is misleading and should be abolished in favor of terms and concepts based on developmental physiology.

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PIGMENTED PAPILLOMA OF SKIN

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There is perhaps no group of tumors about which so much confusion exists as those designated by the term "common mole." Traub and Keil [1] restrict the designation "common mole" to those tumors of the skin which are characterized histologically by the so-called nevus cells. They reserve the term "nevus" for a variety of cutaneous lesions which they differentiate by qualifying adjectives (intraepidermal nevus, blue nevus, nevus verrucosus linearis, and so on), although histologically the tumors so designated may or may not be composed of nevus cells. The term "mole" has been so loosely applied both by the laity and by members of the medical profession that its continued use by the latter group is only to be deplored. At present "mole" may indicate such widely differentiated growths, histologically speaking, as nevus, hemangioma, fibroma, neurofibroma, verruca and melanoma.

It would seem that much of the confusion could be avoided, at least by pathologists and dermatologists, by discarding the term "mole" entirely. The tumors heretofore included in that heterogeneous group could then be designated by more specific names, based on morphologic or histologic criteria. There is no logical reason why a tumor which is composed of what are generally known as nevus cells should be called by any name other than "nevus," or why any tumor which does not contain nevus cells should bear the name "nevus," regardless of how well that term might be elaborated by qualifying adjectives. I disagree with Traub and Keil [1] when they say that "popular usage has fixed the term mole in nomenclature." The mere fact that they find it necessary to define the term in great detail and choose to have it represent a "cellular nevus" proves that the name has no fixed meaning but is "all things to all men" and had best be discarded.

Included within the heterogeneous group of pigmented cutaneous tumors which have been lumped together in the nevus category is the so-called intraepidermal epithelial nevus.[2] The tumor so named has masqueraded under a variety of terms, the most popular of which in addition to "intraepidermal epithelial nevus" are Bloch's "benign pigmented epithelioma" [3] and "intraepidermal nevus." [1] Because of the variety of names by which this tumor is known, it is exceedingly difficult to trace it in the literature. The earliest reference is attributed to Bruno Bloch,[3] who called it "benign pigmented epithelioma." Aside from the fact that the choice of name is a poor one because of the benign versus malignant (epithelioma) connotation, perusal of Bloch's paper reveals that in 1 of the 4 original cases in which he designated a tumor by this name the tumor had no rightful claim to it (case 1). Bloch pointed out very clearly that the pigmented cells in his first case were melanoblasts, while those in his second, third and fourth cases were epithelial cells of the basal layer of the epidermis. He emphasized the fact that melanoblasts were not present in cases 2, 3 and 4, and advanced Miescher's [4] theory, which postulates

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1. Traub, E. F., and Keil, H.: Arch. Dermat. & Syph. **41**:214, 1940.
2. McKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, The American Journal of Cancer, 1937, p. 60.
3. Bloch, B.: Arch. f. Dermat. u. Syph. **153**:20, 1927.
4. Miescher, G.: Virchows Arch. f. path. Anat. **264**:86, 1927.

an origin of melanoblasts from basal cells, to explain their absence. Miescher's theory is at variance with the more widely accepted Masson [5] theory concerning the origin of melanoblasts, but it is not my purpose to contribute to the dispute. The fact remains that Bloch's first case showed melanoblasts and his other cases did not.

The primary purpose of this paper is to report a small group of cases of a pigmented tumor similar to that which Bloch called "benign pigmented epithelioma and others [6] a type of nevus. I hope to make it clear that this tumor, which I shall call pigmented papilloma of skin, has been erroneously classified in the nevus group. As already pointed out, only tumors which contain nevus cells can be classified as nevi; this excludes the "intraepidermal epithelial nevus," which is composed of epithelial cells. According to Dorland's "American Illustrated Medical Dictionary," [7] a papilloma is "an epithelial tumor in which the cells cover finger-like processes or ridges of stroma." The tumor to be described meets these criteria and therefore must be considered to be a papilloma. The feature which distinguishes it from other papillomas is the presence of varying amounts of pigment within the epithelial cells. I can think of no better name for a cutaneous papilloma which contains pigment than pigmented papilloma of skin.

REPORT OF CASES [8]

CASE 1.—A white man 41 years of age had a papillary pigmented tumor of the skin on his "back," which had been present since birth. He had not observed any change in its size or shape during that time. Examination revealed on the skin of the "back" a well circumscribed, densely villous gray-brown nodule, 1.5 cm. in diameter. Excision was performed with the region under local anesthesia.

CASE 2.—A white man 52 years of age was admitted to the hospital with two cutaneous tumors. Examination disclosed several enlarged lymph nodes in the inguinal region. One tumor proved to be a so-called blue nevus. The inguinal lymph nodes were the site of metastases from a melanoma, the primary site of which had not been determined. The pathologist was emphatic in his opinion that neither the "blue nevus" nor the second cutaneous tumor, which was of the type under discussion, was related to the metastases in the lymph nodes.

The second cutaneous tumor was situated on the right side of the neck. It was oval and flattened so that it vaguely resembled a button. It measured 12 mm. in longest diameter at the base. The external surface was dark brown and on close examination was found to be composed of several narrow, firm stalks, which were marked by numerous yellow pinpoint flecks.

CASE 3.—A white woman 49 years of age had a "mole" on the left side of the neck at the anterior border of the trapezius muscle. The lesion was first noticed "one year before." Occasional trauma caused a "stabbing pain" for a short period. Examination disclosed a slightly elevated papillary nodule, which had a uniform dark blue color. It measured 3 mm. in diameter at the base. Wide excision, with the region under local anesthesia, was performed.

CASE 4.—A white man 75 years of age was hospitalized because of obstructive jaundice due to carcinoma of the pancreas. At that time a "warty" mottled tumor of the skin was noted in the left inguinal region. It measured 2.5 cm. in maximum diameter at the base and 4.5 cm. in height. The external surface was coarsely granular and reddish brown. Wide surgical excision was performed.

CASE 5.—A white man 49 years of age, a farmer, had had a tumor of the skin in the right lower quadrant of the abdomen "for fifteen years." The growth was shaped like a mushroom and measured 2.3 by 1.2 by 0.3 cm.; it was attached to the skin by a narrow pedicle, 2 mm.

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5. Masson, P.: (*a*) Bull. Assoc. franç. p. l'étude du cancer, 1921, p. 303; (*b*) Ann. d'anat. path. **3**:417, 1926.

6. Traub and Keil.[1] McKee and Cipollaro.[2]

7. Dorland, W. A. N., and Miller, E. C. L.: The American Illustrated Medical Dictionary, ed. 19, Philadelphia, W. B. Saunders Company, 1941.

8. Dr. M. N. Richter, of the department of pathology, and Dr. T. DeCholnoky, of the department of surgery, of the New York Post-Graduate Medical School and Hospital, gave me permission to use cases 1 and 2.

long. The external surface was gray-tan and coarsely granular. Excision was performed preparatory to appendectomy.

CASES 6, 7 AND 8.—Single histologic sections from 3 other tumors were available. Two of the sections were from tumors of women aged 40 and 63 years, respectively. The third section was found in a dermatologic collection of teaching slides as an example of a "pigmented nevus," about which specific information was lacking.

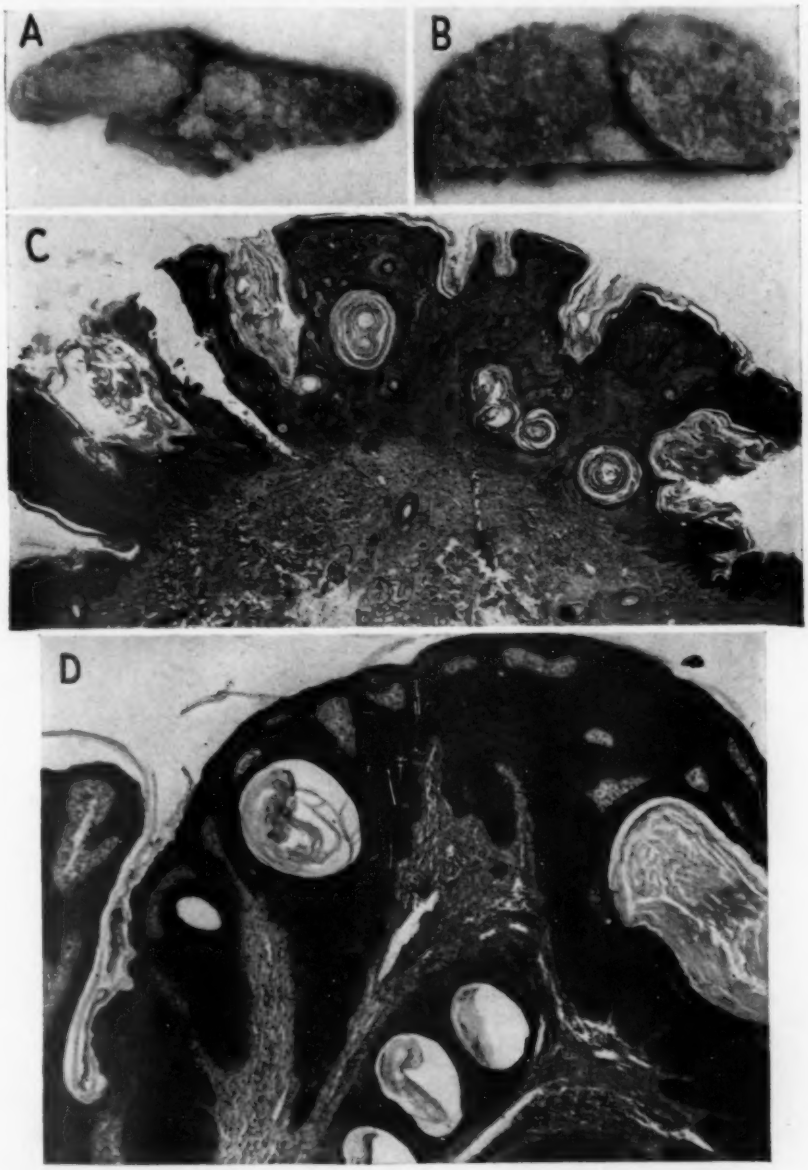

Fig. 1.—*A* and *B* (case 5), gross specimen of pigmented papilloma of skin. The tumor has a tan color and a coarsely granular surface. *A* is a lateral view to illustrate the pedicle. *B* shows the superior surface of the tumor after a portion had been removed for histologic examination. × 3. *C* (case 8), low power view of a section of the tumor to illustrate its papillary configuration. Note the deep crypts filled with keratin and the keratin masses in cross section. × 12. *D* (case 2), a section of pigmented papilloma of skin, showing limitation of the tumor cells and the melanin to the epidermal layer. × 20.

MORPHOLOGIC DESCRIPTION

The gross and microscope features of the tumor as observed in these cases are summarized in the following paragraphs. The tissues were fixed in either 4

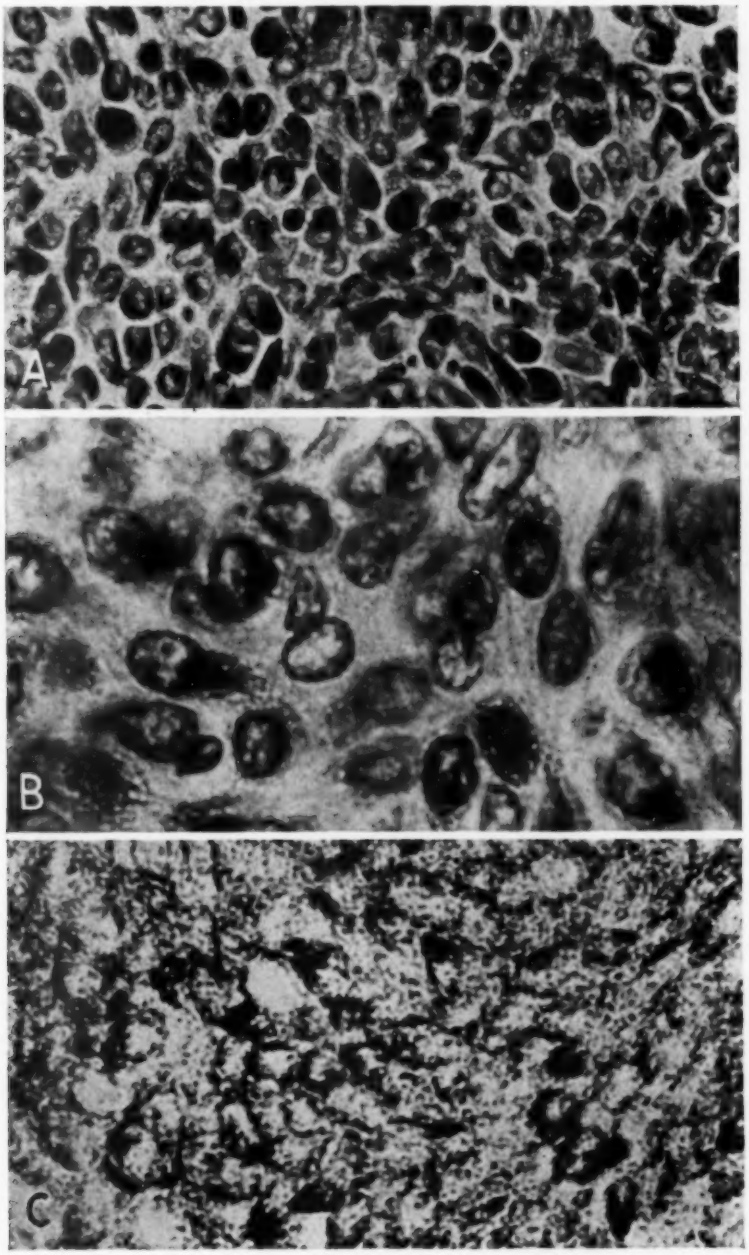

Fig. 2.—*A* (case 2), tumor cells, many of which are filled with melanin. In some cells the deposits of pigment have pushed the nucleus to one side. × 450. *B* (case 2), oil immersion to show morphologic features of the cells and deposits of pigment. The intercellular bridges are not illustrated clearly. × 950. *C* (case 3), tumor cells containing melanin stained black with silver (Bielschowsky). × 450.

per cent solution of formaldehyde or Bouin's solution; blocks were impregnated with paraffin following dehydration in alcohol, and sections were stained with hematoxylin and eosin.

Pigmented papilloma of skin varies somewhat in its gross characteristics but usually has a papillary configuration. In some instances it may have a polypoid button shape because of continued pressure of clothing or because of other constant trauma tending to flatten the villi. The base is round or oval and may range from 0.5 to 3.0 cm. in diameter. The tumor is elevated from 0.5 to 1.5 cm., as a rule, but may rise to 4.5 cm., as it did in case 4. The papillomatous portion is composed of a number of villi, from two to six, the length of which may be uniform or not. These villi give the growth a "warty" appearance. The color of the tumor varies in direct proportion to the amount of pigment present. The majority vary from light tan to dark brown; those which contain pigment in abundance take on a bluish black shade.

Microscopically, the outstanding feature, and the one which clearly differentiates the pigmented papilloma of skin from the nevus, is its intraepidermal location. The entire growth is confined within the epidermis and does not penetrate the basal layer at any point. The surface layer is very irregular. It is marked by tall peaks and deep crevices, which extend for varying distances below the plane of the epidermis. This configuration accounts for the papillary gross appearance of the majority of the tumors of this group, and even those which may have appeared to be smooth grossly show some tendency toward papillary structure under the microscope. The surface epithelium, particularly within the papillary crypts, is hyperkeratotic; in places these keratotic areas are sectioned in such a way as to appear as inclusion cysts filled with keratin.

The cellular portion of the tumor is arranged in large and small confluent nests of closely packed epithelial cells. The cells are either round or oval and bear a striking resemblance to those of the basal layer of the epidermis. The cellular nests are separated from each other by slightly irregular columns of collagenous connective tissue, which may be sprinkled with inflammatory cells, especially lymphocytes. The cells which comprise the major portion of the tumor are of medium size, perhaps slightly larger than the normal cells of the basal epidermal layer. They are separated from their neighbors by well defined intercellular bridges, a feature which definitely establishes their epithelial heritage. The nucleus is single and round or oval, and occupies from one half to three quarters of the cell body. It has a very prominent, centrally placed nucleolus from which the deeply basophilic chromatin material radiates in spoke fashion. The nucleus is surrounded by a narrow collar of homogenous eosinophilic cytoplasm, which in turn is enclosed within a well demarcated cell membrane. The cytoplasm of a varying number of cells, depending on the particular tumor, contains deposits of finely granular golden brown pigment. In some cells the pigment may be so abundant that the nucleus is pushed to one side. Mitotic figures are not present. The pigment was verified as melanin by special staining. It appeared as a rich golden brown in the hematoxylin and eosin preparation. In the cases in which tissue was available for further study, silver staining (Bielschowsky) failed to reveal melanoblasts, nor was their presence suggested in the hematoxylin and eosin preparations. The silver stained the pigment black. The pigment did not stain for iron (berlin blue).

COMMENT

It becomes apparent that this tumor is a papillary growth of the skin composed of epithelial cells which resemble the cells of the basal layer of the epidermis. It

is distinguished from other papillomas by the presence of melanin pigment within the epithelial cells. It cannot be considered a nevus for two principal reasons: (*a*) the absence of cells which are generally known as nevus cells and (*b*) its intraepidermal location.

Judging from the small group of cases reported here, it is found most commonly in the older age groups (table). The patients were 40, 41, 49, 49, 52, 63 and 75 years; the age of 1 patient was not known. The patient whose case was reported by Traub and Keil [1] was a white woman of 37 years. The patients in Bloch's [3] second and third cases were white men aged 50 and 54 years. Males and females were involved with about equal frequency. So far as is known, all patients referred to here were white, but in all probability a similar tumor occurs in Negroes.

Pigmented papilloma of skin apparently has no predilection for any particular region of the body. In 2 cases it was situated on the neck; in 2, on the abdomen, and in 1, on the "back." The location in 3 cases is not known. (In 1 of the latter cases apocrine sweat glands were noted in the microscopic section, suggesting a possible origin in the axillary or the anogenital region.) No case is known in which the tumor occurred on the extremities. The patient of Traub and Keil had the tumor on the cheek for nineteen years. In Bloch's second case the tumor was on the wall of the chest, and in his third case it was on the forehead. (His first case, which does not belong in this group for reasons already discussed was one of multiple tumors.)

Data in Eight Cases of Pigmented Papilloma of Skin

Case	Age	Sex	Color	Site	Duration	Size, Cm.	Color
1	41	M	W	Back	Since birth	1.5	Gray-brown
2	52	M	W	Neck	.....	1.2	Brown
3	49	F	W	Neck	1 year	0.3	Blue
4	75	M	W	Inguinal region	.....	2.5 by 2.0 by 4.5	Red-brown
5	49	M	W	Abdomen	15 years	2.3 by 1.2 by 0.3	Tan
6	40	F	W	.....	.....	.....	.....
7	63	F	W	.....	.....	.....	.....
8	..	..	..	.....	.....	.....	.....

The size of the tumor in the cases reported varied from 0.3 to 2.3 cm. in maximum diameter at the base. The average elevation was 2 to 3 mm., although in case 4 the tumor was so raised (4.5 cm.) that it appeared as a finger-like projection. In all the cases it had a more or less marked papillary structure, which in 1 or 2 instances was flattened into a button shape. In 1 case (5) the tumor was pedunculated.

Pigmented papilloma of the skin is benign, and there is no evidence to suggest cancerous potentialities. The presence of metastic melanoma in the inguinal lymph nodes in case 2 is considered coincidental and unrelated to this tumor.

SUMMARY

Eight cases of a tumor of the skin heretofore known by a variety of names and classified in the "nevus" group are reported (5 in detail). The tumor is epithelial in origin and is in no way related to tumors of the skin composed of nevus cells.

The names previously applied to this tumor are discussed and are believed to be misnomers. Because of the epithelial origin, the location, the papillary structure and the pigment content, the name "pigmented papilloma of skin" is considered compatible with the morphologic and histologic features of the growth.

A plea is made, especially to pathologists and dermatologists, to discard the term "mole" and to reserve the name "nevus" for tumors of the skin which are composed of "nevus cells."

INTIMAL CHANGES IN MEDIAL DEGENERATION OF THE AORTA

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AND
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The usual thickening, puckering and wrinkling of the aortic intima producing the so-called tree bark effect almost invariably indicates the presence of syphilitic mesaortitis. In 1939 one of us (A. R.) presented a case of aneurysm occurring in a 70 year old woman.[1] Though the intima presented a typical syphilitic appearance, microscopic examination revealed absence of syphilitic mesaortitis and presence of medial degeneration. The case to be described in this paper is similar with the exception that spontaneous rupture occurred.

It was deemed advisable to add the present report to the literature because nothing further seems to have been written on this phase of the subject, even though in some teaching circles it appears to be known that medial degeneration may alter the intima and lead to a false diagnosis of syphilis. Thus in the "Nomenclature and Criteria for Diagnosis of Diseases of the Heart"[2] one reads in the chapter pertaining to medial degeneration ". . . focal defects in the media with thinning of the muscle layer, covered by a somewhat wrinkled intima. These lesions may be confused with foci of syphilitic mesaortitis." Gsell,[3] in describing his first case of spontaneous rupture of the aorta, mentioned fine wrinkling of the intima as a macroscopic alteration over an area of medial degeneration. He paid no further attention to the intima except to emphasize the almost complete absence of change in it. Erdheim,[4] Cellina,[5] Levinson,[6] Wolff[7] and Neuberger[8] either make no mention of intimal alteration or emphasize the smoothness of the intima and its freedom from sclerosis.

Relative to the error that may result in confusing macroscopically medial degeneration with syphilis one need only read Erdheim.[4a] According to his own statement, he occasionally used cases of medial degeneration in teaching the pathology of syphilis of the aorta. It was not until he subjected such a case to microscopic study that he became aware of his mistake. One wonders, too, whether Shennan[9] might not have been in error when he accepted from the literature

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1. Rottino, A.: Arch. Path. **27**:320, 1939.

2. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association Criteria Committee, ed. 4, New York, New York Tuberculosis and Health Association, Inc., 1939.

3. Gsell, O.: Virchows Arch. f. path. Anat. **1**:270, 1928.

4. Erdheim, J.: (*a*) Virchows Arch. f. path. Anat. **273**:454, 1929; (*b*) **276**:187, 1930.

5. Cellina, M.: Arch. ital. di anat. e istol. pat. **2**:1105, 1931.

6. Levinson, B.: Virchows Arch. f. path. Anat. **282**:1, 1931.

7. Wolff, K.: Virchows Arch. f. path. Anat. **285**:1, 1932.

8. Neuberger, K.: Ztschr. f. Kreislaufforsch. **24**:169, 1932.

9. Shennan, T.: Dissecting Aneurysm, Medical Research Council, Special Report Series, no. 193, London, His Majesty's Stationery Office, 1934.

as syphilitic 8 cases of dissecting aneurysm solely on the basis of intimal change, in the absence of histologic studies.

That scant attention has been given to possible intimal alterations secondary to medial degeneration of the aorta is not at all surprising, for the intima in each of the various cases reported was usually smooth. Furthermore, the authors were primarily interested in the medial lesion, its genesis, causation and relation to spontaneous rupture.

REPORT OF A CASE

A 60 year old Negro was admitted to St. Vincent's Hospital, in New York, June 3, 1941, acutely ill. An hour before, he had been seized with substernal pain, accompanied by dyspnea, pallor, cold sweat and hemoptysis.

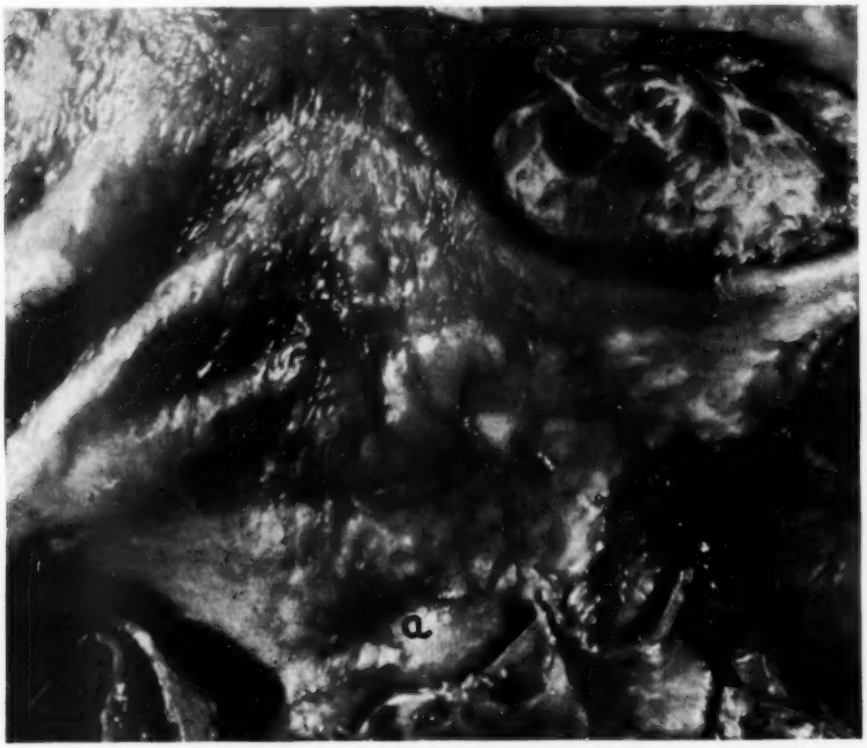

Fig. 1.—Aorta with a spontaneous rupture. Note the puckering of the intima at *a* and the pronounced wrinkling elsewhere.

There was a history of syphilis contracted twenty-five years before, for which he received treatment. He had also undergone posterior gastroenterostomy for an alleged peptic ulcer.

He appeared to be in severe pain. The pupils were small, equal and reacted to light and in accommodation. There was slight injection of the throat. The lungs were normal except for diminished breath sounds over the lower lobe of the left lung. A systolic murmur could be heard over the precordium. The pulse rate was 88 per minute; the rhythm was regular; the blood pressure was the same on both sides, 160 systolic and 105 diastolic. The liver was felt two fingerbreadths below the costal border. There was no peripheral edema. The reflexes were normal. The eyegrounds presented no unusual change.

On admission the patient had a temperature of 99.9 F. On the third and fourth days the blood pressure readings were 144 systolic and 88 diastolic and 136 systolic and 96 diastolic. By the fifth day the cardiac rhythm had changed to auricular fibrillation. On the sixth day the patient collapsed suddenly and died.

Urinalysis gave normal results. The Kahn test of the blood was negative. The white blood cell count on admission was 7,900, with 70 per cent polymorphonuclear leukocytes, 14 per cent lymphocytes, 8 per cent metamyelocytes and 8 per cent monocytes. Roentgen examination of the chest revealed an enlarged cardiac shadow and a broadening of the mediastinum, arousing a suspicion of aneurysm.

Necropsy.—The ascending aorta was considerably dilated. Two centimeters above the free borders of the cusps of the aortic valve was a transverse tear through the intima and media

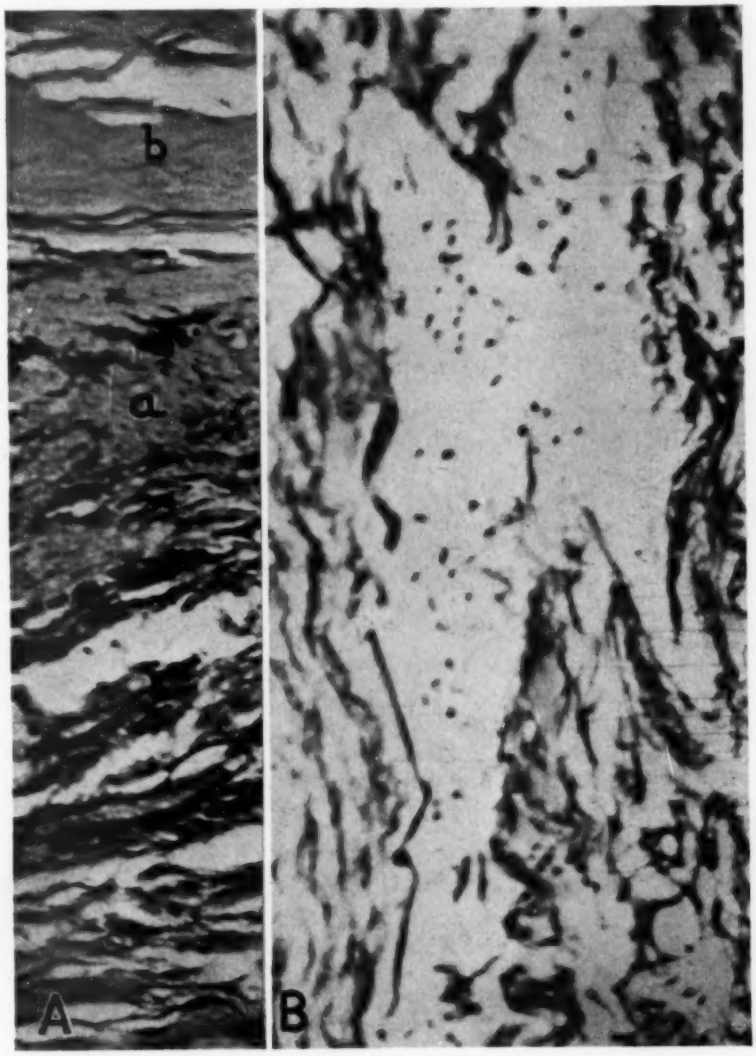

Fig. 2.—*A*, photomicrograph of aortic media showing elastic tissue stain of an area of medial degeneration. Note the defect produced by loss of elastic tissue (*a*). The overlying intima is thick because of fibrosis (*b*). *B*, reticulum stain of an area of medial degeneration. Note the complete loss of all tissue with the resulting cystic defect.

extending obliquely upward toward the arch (fig. 1). Its edges were rolled and smooth. No dissection was grossly visible. The base of the ruptured portion of the aorta was formed by a bulging, thrombus-filled sac, lined by adventitia, which at one point contained a perforation leading into the pericardial sac. One half centimeter above the posterior cusp the surface of the intima was deeply puckered. From just beyond this point to the arch the intima

was wrinkled and contained raised silvery plaques which gave to it a tree bark appearance. Beyond the arch one found occasional atherosclerotic plaques. The heart itself was diffusely hypertrophied, chiefly in the left ventricle. All valves were essentially normal. The myocardium appeared unchanged. Atheromatous plaques were found in the coronary arteries. The pericardial sac was filled with blood. The liver was red-brown and weighed 2,100 Gm. The spleen, the pancreas, the adrenal glands, the prostate gland and the testes were normal. Stones filled the gallbladder. Except for the evidence of an old posterior gastroenterostomy the gastrointestinal tract was normal. The lungs were congested. Together the kidneys weighed 340 Gm. Both were diffusely granular and red. The cortex of each was slightly narrowed.

Microscopic Examination.—The whole of the aorta from the aortic ring to the lower thoracic portion was completely cut into blocks (thirteen) in such a manner that each included the entire circumference of the vessel.

There were numerous focal areas of medial degeneration distributed about the entire circumference from just above the aortic valve to approximately 1 cm. below the isthmus. Beyond this point medial degeneration appeared absent. Within the media the lesions were seen chiefly in the inner and middle thirds. Many, however, occupied its entire width. In sections stained with hematoxylin and eosin they appeared as areas devoid of muscle cells. With Weigert's elastic tissue stain one further saw complete disintegration of elastic lamellas (*a* in fig. 2*A*). In addition, in some areas the reticulum showed various degrees of alteration from simple loss of waviness to complete dissolution (fig. 2*B*). Where the latter had occurred, gaps resulted, occupied by a homogeneous substance staining pink with eosin, brown with silver, green with brilliant green. An occasional one of these was filled instead by a few loosely arranged stellate cells, fibroblasts. Nowhere were vascularized scars found such as are seen in syphilis. Nowhere was cellular reaction discernible. A few small narrow

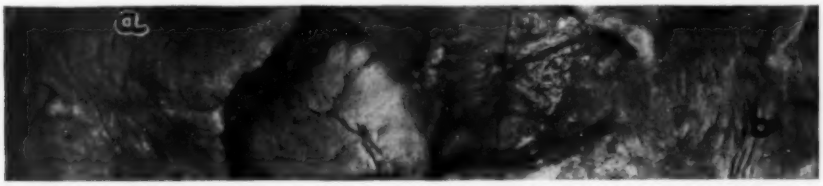

Fig. 3.—Old healed dissecting aneurysm of the ascending aorta. Note linear wrinkling at *a* and *b*.

scars were found containing thin-walled vascular channels, but these lay beneath atherosclerotic plaques.

There was a diffuse hemorrhage in the adventitia. In many areas fibroblastic proliferation was marked, and in others there was dense infiltration by polymorphonuclear leukocytes. Vasa vasorum failed to show endarteritis.

The intima was diffusely thickened, owing to increase of fibrous tissue (*b* in fig. 2*A*). In places raised hyalinized plaques were present. A few had fatty deposits beneath them. Much of the intimal thickening was observed over areas of medial degeneration. In other areas, however, the underlying media was normal.

Microscopic examination of other organs showed myofibrillar hypertrophy, epicardial hemorrhage, mild arteriolosclerosis of the pancreas, normal adrenal and prostate glands, congestion of the lungs, mild chronic passive congestion of the liver and marked congestion and arteriosclerosis and arteriolosclerosis of the kidneys.

The anatomic diagnosis was medial degeneration of the aorta with spontaneous rupture, hypertrophy and dilatation of the heart, cholelithiasis, arteriolonephrosclerosis, bilateral hydrocele, bilateral hydrothorax and old posterior gastroenterostomy.

COMMENT

In syphilis the intimal changes which impart to the aorta a tree bark appearance are a combination of retraction, wrinkling, fibrous thickening and plaque formation of the inner surface. Though these alterations of the intima had been described by 1850,[10] it was not until the specificity of syphilitic mesaortitis had been estab-

10. Dittrich, F.: Beiträge zur pathologischen Anatomie der Lungen-Krankheiten, Erlangen, L. Bloesing, 1850; cited by Doehle.[12]

lished that they became regularly accepted as indicating invariably an underlying syphilitic disease. Concerning its genesis a few [11] have felt that in some cases at least the cause lay in direct infection of the intima by spirochetes. Doehle [12] expressed the belief that an occasional intimal plaque directly continuous with a medial scar might be the result of direct spread to the intima from the media of the syphilitic noxa. In the main, however, he agreed with Dittrich [10] that the intimal lesions of syphilis are due to altered tension resulting from medial changes. Most writers appear to have accepted this teaching, explaining the phenomenon of intimal thickening as compensatory, an attempt on the part of the intima to bolster a wall weakened by destruction of its middle coat. If such an explanation is true, then any destructive disease of the media should in time lead to intimal change. As to our present case, we subscribe to this line of reasoning and ascribe the intimal changes to abnormal tensions arising from focal mural weakening caused by idiopathic medial degeneration. To be sure, narrow vascularized scars were found in the media, but these lay beneath thick atherosclerotic plaques and were of the type accepted since the time of Chiari [13] as secondary to the intimal lesion. With a history of treated syphilis in our case one cannot ignore entirely the possibility of primary syphilitic intimitis. In refutation of this we must cite the first case described by one of us [1] in which the aorta except for the rupture presented an appearance identical with that of the aorta herein described. This patient was a woman aged 70 in whom there was no clinical or pathologic evidence of syphilis.

A word should be said on the incidence of intimal changes ascribed to medial degeneration. In a series of 210 nonruptured aortas [14a] carefully studied 7 were found showing medial degeneration. In 4 the intima was smooth; 2 contained scattered atheromatous plaques and 1 exhibited severe fibrosis. In the latter the appearance was not syphilitic. In a series of 12 aortas with spontaneous rupture [14b] there were 2 in which the intima was thick and wrinkled. One of the cases had been considered for a long time as one of dissecting aneurysm occurring in a syphilitic aorta. Both cases were exceedingly chronic, for the ruptures were found completely healed (fig. 3).[15] Clinical data were not available in either case. It would seem that the factors necessary if intimal lesions are to appear are extensive medial lesions present for a long period. Thus, with focal points of weakness and strain, local fibrosis would follow given sufficient time.

SUMMARY

A report of a case of severe medial degeneration of the aorta with a tree bark type of intima is presented. Syphilitic mesaortitis and endoarteritis obliterans of the vasa vasorum were not present. It is contended that the intimal lesion in this case is not syphilitic and is secondary to mural weakness resulting from medial degeneration.

Brief mention is made of the incidence of intimal lesions in cases of medial degeneration.

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11. McMeans, J. W.: Am. Heart J. **6**:42, 1930.
12. Doehle, P.: Ein Fall von eigentümlicher Aortenerkrankung bei einem Syfilitischen, Inaug. Dissert., Kiel, Schmidt u. Klaunig, 1885.
13. Chiari: Verhandl. d. deutsch. path. Gesellsch. **15**:137, 1903.
14. Rottino, A.: (*a*) Am. Heart J. **19**:330, 1940; (*b*) Arch. Path. **28**:1, 1939.
15. The specimen was received from the office of the Medical Examiner, New York (Thomas A. Gonzales, M.D., chief).

QUANTITATIVE STUDY OF CORRELATION BETWEEN BASOPHILIC DEGENERATION OF MYOCARDIUM AND ATROPHY OF THYROID GLAND

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A perusal of the papers on basophilic degeneration of the myocardium revealed no cases of atrophy of the thyroid gland analyzed for this lesion. The impression has been gained by us that a correlation exists between basophilic degeneration of the myocardium and atrophy of the thyroid gland. With this in mind, 8 cases of atrophy of this organ (including 6 of myxedema and 2 of polyglandular atrophy) were compared with 142 control cases, in order to study this problem. The study demonstrated that, although basophilic degeneration of the myocardium occurs in other conditions, it is more pronounced in diseases in which the thyroid gland is atrophic. No attempt has been made to explain the mechanism of basophilic degeneration or to determine whether this lesion is important in severe hypothyroidism.

REVIEW OF LITERATURE

In a paper on rheumatic myocarditis, Geipel [1] described the case of a 16 year old girl with rheumatic pancarditis. In the myocardium were areas of blue-staining muscle fibers. He thought that the muscle fibers were impregnated by stained material diffused from their nuclei.

Saigo [2] found a peculiar blue-staining quality in the Purkinje fibers of the hearts of 4 persons, 1 with sarcoma of the lung and 3 with carcinoma of various sites.

Hewitt [3] noted small round oval or irregular, pale blue areas within single heart muscle fibers. This lesion was present in a case of tertiary syphilis with gummas in the brain and in a case of appendectomy with acute serofibrinous peritonitis, thrombophlebitis of the portal vein and multiple abscesses of the liver.

Haumeder [4] studied sections from the ventricular walls and the septum of the heart in 320 cases, in 107 (30 per cent) of which were areas of basophilic degeneration, a term first employed by her and adopted by subsequent authors. The various stains applied indicated that the areas of degeneration contained mucin as well as a component related to glycogen. Of the 107 persons with basophilic degeneration of heart muscle fibers, 95 were in the age group of 40 to 80 years. The lesion was found in 37 of 81 cases of cancer, in 21 of 52 cases of heart disease, in 9 of 20 cases of cholecystitis and cholelithiasis, in 6 of 16 cases of gastrointestinal ulcers, in 9 of 16 cases of pneumonia, in 5 of 15 cases of peritonitis, in 4 of 21 cases of tumor of the brain, in 4 of 9 cases of syphilis, and in 4 of 7 cases of genitourinary infection.

From the Department of Pathology, University of Colorado School of Medicine and Hospitals.

1. Geipel, P.: Deutsches Arch. f. klin. Med. **85**:75, 1905.
2. Saigo, Y.: Verhandl. d. deutsch. path. Gesellsch. **12**:165, 1908.
3. Hewitt, J. H.: Bull. Johns Hopkins Hosp. **21**:278, 1910.
4. Haumeder, M. E.: Am. J. Path. **11**:535, 1935.

Of the 50 hearts studied by Liebegott,[5] 42 per cent showed basophilic degeneration of muscle fibers. He discussed the condition etiologically with regard to age, sex, occupation and cause of death but arrived at no definite explanation of it.

In the 83 hearts examined by Umeda[6] with Patzelt's stain, 60 revealed "so-called basophilic degeneration" of the heart muscle. In 145 hearts (presumably including the 83 mentioned) he found an incidence of 80.7 per cent (117) with Bauer's stain. He did not tabulate the diseases associated with the lesion nor the decades of life in which it was present. He proposed the term "mucoid degeneration of the heart."

Of the 66 necropsies reviewed by Cardoso,[7] 14 had disclosed basophilic degeneration of the heart muscle fibers. The patients were 15 days to 100 years old, but the ones with positive findings were seen between the ages of 27 and 75 years. She found no relation between the presence of the lesion and the time elapsing between death and postmortem examination.

MATERIALS AND METHODS

Most of the tissue sections had been fixed in Zenker's fluid and were stained with hematoxylin and eosin. Sections from the left ventricle or from the intraventricular septum or from both or from these two locations and the right ventricle were obtainable in the 150 cases studied. Except in 8 instances (3 of atrophy, 3 of hyperplasia and 2 of carcinoma of the thyroid gland), the cases were chosen at random from the 1,155 autopsies at the Colorado General Hospital from Jan. 1, 1939 to Dec. 31, 1942. Seven of the 8 cases were from the earlier necropsy files of the same institution. The eighth was a case of polyglandular atrophy which Dr. K. T. Neubuerger allowed us to use and which will be reported by him in detail later. Sections of the thyroid gland were studied in the 8 cases of atrophy of that organ and in most of the 142 control cases.

The control cases were divided into sixteen groups including (1) acute infections, 10; (2) accidents, 10; (3) nephritis, 9; (4) gastrointestinal ulcers, 9; (5) rheumatic heart disease, 10; (6) cerebral hemorrhage, 10; (7) arteriolosclerosis of the kidneys, 9; (8) silicosis, 9; (9) cholecystitis, 9; (10) chronic infections, 12; (11) arteriosclerotic heart disease, 11; (12) cancer, 13; (13) diabetes, 9; (14) cirrhosis of the liver, 5; (15) hyperplasia of the thyroid gland, 5, and (16) carcinoma of the thyroid gland, 2. Of the 142 patients, only 4 (2 with cirrhosis of the liver and 2 with hyperplasia of the thyroid gland) were under 40 years of age. The sex of 97 was male; that of 45, female. Of the 142 control cases, 67 revealed basophilic degeneration of the myocardium to some degree, usually minimal. In these 67 cases, one section of heart was available in 13, two in 31, three in 12, four in 8 and five in 3 cases. In each section the number of myocardial fibers affected by basophilic degeneration was counted. The total obtained was divided by the number of sections to determine the average number of fibers in each case. The average number of fibers for each of the sixteen groups was calculated by dividing the total of the average numbers of fibers for all cases in the group by the number of cases in the group.

On the average, less than 5 fibers were affected in 56 of the 67 positive control cases. The remaining positive 11 control cases, showing an average of 5 or more fibers with this method, included 3 of cancer, 2 of chronic infection, 2 of arteriosclerotic heart disease and 1 each of cerebral hemorrhage, silicosis, cholecystitis and diabetes. The number of myocardial fibers affected by basophilic degeneration in these 11 cases and in the 8 cases of atrophy of the thyroid gland was calculated by a strict quantitative method. A number 10 micrometer ocular was calibrated with a Neubauer bright line counting chamber so that a field 857.1 microns by 450 microns or 385,695 square microns was obtained. Fifty of these fields, or 19,284,750 square microns (19.28 square millimeters), were counted in each case. The third dimension was constant since the thickness of each section was 6 microns. In each case the total number of myocardial fibers affected by basophilic degeneration in this area of 19.28 square millimeters was called the basophilic degeneration index (B. D. I.). So far as possible, only groups of intact muscle fibers were scanned, exclusive of scars, large blood vessels, areas of intermuscular adipose tissue infiltration and areas of inflammation or other pathologic involvement. Fields containing fibers cut longitudinally were favored, although the inclusion of many fields of fibers cut transversely or tangentially was impossible to avoid.

5. Liebegott, G.: Beitr. z. path. Anat. u. z. allg. Path. **98**:410, 1937.
6. Umeda, K.: Virchows Arch. f. path. Anat. **307**:1, 1940.
7. Cardoso, R. A. de A.: Mem. Inst. Oswaldo Cruz **35**:495, 1940.

DESCRIPTION OF LESION

In a section of affected heart muscle stained with hematoxylin and eosin, the areas of basophilic degeneration are cigar shaped in muscle fibers cut longitudinally and rounded or oval in muscle fibers cut transversely or tangentially. The muscle fiber is swollen at the site of the degenerated zone. In the pale to dark basophilic area of degeneration, the cross striations are lost and the longitudinal striations disappear partially or completely, depending on the extent of the lesion. The striations disrupted are intermingled in the basophilic stuff as short irregular wavy acidophilic fibrils or as acidophilic granules, singly or in small clumps. The degenerated areas frequently contain more or less pyknotic nuclei of muscle fibers as well as granules of lipochrome pigment. Between the degenerated area and the surrounding sarcoplasm with intact longitudinal and cross striations there may be a clear zone of shrinkage, particularly in the more advanced or large lesions.

TABLE 1.—*Summary of Data on Control Cases*

Group	Anatomic Diagnosis	Cases	Cases with Basophilic Degeneration of Heart Muscle Fibers	Average Number of Fibers Involved per Group	Males	Females	Age		
							Minimum	Maximum	Average
1	Acute infection	10	0	0.00	10	0	41	91	63.2
2	Accident	10	1	0.05	8	2	41	79	58.1
3	Nephritis	9	4	0.35	5	4	42	70	57.2
4	Gastrointestinal ulcers	9	5	0.42	7	2	45	71	59.1
5	Rheumatic heart disease	10	5	0.43	3	7	45	72	53.4
6	Cerebral hemorrhage	10	6	0.76	7	3	47	79	66.0
7	Arteriolosclerosis of kidneys	9	6	0.87	5	4	41	67	54.8
8	Silicosis	9	2	1.26	9	0	53	74	61.9
9	Cholecystitis	9	8	1.85	7	2	45	78	62.6
10	Chronic infection	12	7	3.39	10	2	46	79	62.3
11	Arteriosclerotic heart disease	11	5	3.98	9	2	53	78	66.1
12	Cancer	13	9	4.38	7	6	44	76	59.9
13	Diabetes	9	6	4.44	4	5	44	80	60.1
14	Cirrhosis of the liver	5	1	0.13	3	2	22	70	48.2
15	Hyperplasia of the thyroid gland	5	1	0.20	2	3	15	72	39.4
16	Carcinoma of the thyroid gland	2	1	1.00	1	1	54	69	61.5
	Totals	142	67		97	45		Average	59.7
	Incidence of basophilic degeneration, 47.2%.								
17	Miscellaneous group (11 cases from groups 1 through 13)	11	11	16.20	6	5	44	79	63.2

CONTROL CASES

Included in the group of cases of acute infection were 4 of lobar pneumonia, 2 of cellulitis with septicemia and 1 each of bacterial endocarditis, pneumococcic meningitis, lymphocytic meningoencephalitis, and bacteremia due to the gas bacillus. Of the cases of nephritis, 8 were of the chronic and 1 of the subacute type. The locations of the lesions in the cases of gastrointestinal ulcers were gastric in 4, duodenal in 4 and ileal in 1. Cerebral hemorrhage was associated with cerebral arteriosclerosis in 8 cases, with a congenital aneurysm in 1 and with both in 1. Silicosis was uncomplicated in 6 cases and was accompanied by tuberculosis in 3 cases. The cases of chronic infection included 2 of empyema, 2 of bacterial endocarditis, 2 of syphilitic aortitis and 1 each of pulmonary tuberculosis, varicose ulcers, cellulitis and peritonitis. The cases of cancer included 1 of multiple myeloma, 1 of cerebral glioma and 11 of carcinoma (in 2, involving the pancreas; in 2, the stomach, and in 1 each, the lip, the bladder, the prostate gland, the breast, the ovary, the palate and the duodenum). The 5 cases of hyperplasia of the thyroid gland were postoperative.

The data for the control cases is summarized in table 1.

CASES OF ATROPHY OF THE THYROID GLAND

1. Atrophy of the thyroid gland with myxedema, coronary arteriosclerosis and cardiac failure in a man 64 years of age. The basophilic degeneration index was 16.

2. Atrophy and fibrosis of the thyroid gland with myxedema and bronchopneumonia in a woman of 69 years. The basophilic degeneration index was 48.

3. Atrophy of the thyroid gland with myxedema, bronchopneumonia, coronary arteriosclerosis and cardiac hypertrophy in a woman 61 years of age. The basophilic degeneration index was 43.

4. Atrophy of the thyroid gland with myxedema, coronary arteriosclerosis and thrombosis with myocardial infarction and rupture of the left ventricle in a woman 56 years old. The basophilic degeneration index was 12.

5. Atrophy of the thyroid gland with myxedema, fracture of the pelvic bones with diffuse hemorrhage and shock, coronary arteriosclerosis and occlusion with old myocardial infarction, and cardiac hypertrophy and dilatation in a 67 year old woman. The basophilic degeneration index was 62.

6. Atrophy of the thyroid gland with myxedema, coronary arteriosclerosis and cardiac failure in a woman aged 59. The basophilic degeneration index was 50.

7. Polyglandular atrophy including the thyroid gland (with myxedema), adrenal glands, ovaries and pancreas, together with focal pulmonary gangrene, ulcerative esophagitis and subacute colitis, in a woman aged 57. The basophilic degeneration index was 34.

8. Polyglandular atrophy including the thyroid gland, the pituitary gland, the adrenal glands, the testes, the prostate gland and the seminal vesicles, and rheumatic valvulitis with cardiac failure in a man 49 years old. The basophilic degeneration index was 59.

TABLE 2.—*Comparison of Eleven Miscellaneous Control Cases with Eight Cases of Atrophy of the Thyroid Gland*

Group	Anatomic Diagnosis	Cases	Cases with Basophilic Degeneration of Heart Muscle Fibers	Basophilic Degeneration Index	Males	Females	Age		
							Minimum	Maximum	Average
17	Miscellaneous cases from groups 1 through 13	11	11	7.7	6	5	44	79	63.2
18	Atrophy of the thyroid gland	8	8	40.5	2	6	49	69	60.3

COMMENT

In the 11 positive control cases of basophilic degeneration, which showed an average of more than 5 fibers involved when analyzed by the relatively inexact section count method, the average number of fibers per case ranged from 6 to 30, with an average for the group of 16.2. When studied by the exact quantitative method, the cases showed the basophilic degeneration indexes ranging between 5 and 10 and averaging 7.7, a figure less than half that obtained by the first method. This demonstrated that the criteria for the determination of the average number of fibers affected in the positive controls were twice as generous by the first method. Consequently, the figures found for the cases of atrophy of the thyroid gland were even more significant. Of these 11 positive control cases, sections of thyroid gland were available in 10. Four of these were normal, 4 contained one to three groups of enlarged, involuted follicles, and 2 showed moderate interstitial fibrosis, infiltration of the stroma by lymphocytes arranged in scattered foci, and partial atrophy of a few groups of follicles.

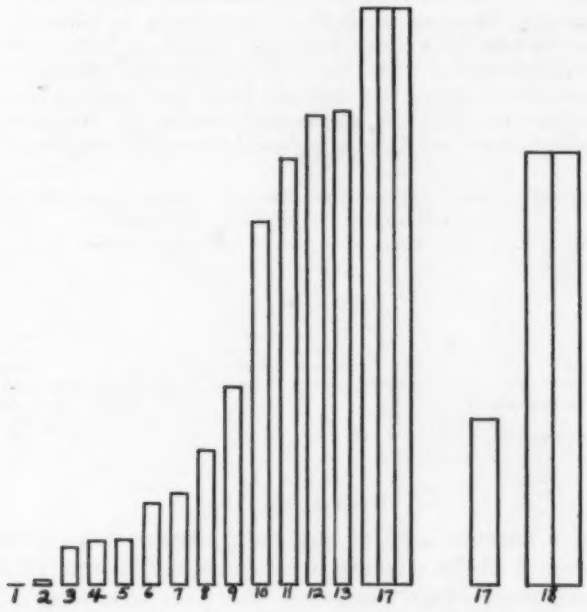
Table 2 summarizes the salient features of the group of miscellaneous control cases and those of the cases of atrophy of the thyroid gland. The average basophilic degeneration index of the cases of atrophy of the thyroid gland was 40.5, compared with 7.7, the average basophilic degeneration index for the miscellaneous control cases. The arithmetic difference between the 2 groups was 32.8 and the geometric difference was 5.03. Mucoid change in the connective tissue was found in none of the 8 cases of atrophy of the thyroid gland.

SUMMARY

A quantitative study has been made of basophilic degeneration of the myocardium in 8 cases of atrophy of the thyroid gland and in 142 control cases, of which 67 showed basophilic degeneration of the myocardium.

The number of muscle fibers affected by basophilic degeneration in an area of myocardium measuring 19.28 square millimeters was designated as the basophilic degeneration index (B. D. I.).

The basophilic degeneration index for the 8 cases of atrophy of the thyroid gland was 40.5 and that for the 11 selected positive control cases was 7.7, showing a quantitative correlation between basophilic degeneration of the myocardium and atrophy of the thyroid gland.



The columns grouped at the left show the results of the analysis of the first thirteen groups of control cases and of the miscellaneous control cases. The numeral at the base of each column corresponds to the number of the group in the first column of table 1. The columns represent the average number of fibers affected by basophilic degeneration in each group of control cases. To conserve space the average number of fibers in group 17 are represented as three columns, which may be superimposed on one another to contrast with the other columns.

The average number of fibers involved per case in each group was as follows: 1. Acute infections, 0.00. 2. Accidents, 0.05. 3. Nephritis, 0.35. 4. Gastrointestinal ulcers, 0.42. 5. Rheumatic heart disease, 0.43. 6. Cerebral hemorrhage, 0.76. 7. Arteriolosclerosis of the kidneys, 0.87. 8. Silicosis, 1.26. 9. Cholecystitis, 1.85. 10. Chronic infections, 3.39. 11. Arteriosclerotic heart disease, 3.98. 12. Cancer, 4.38. 13. Diabetes, 4.44. Group 17 (11 miscellaneous cases from groups 1 through 13), 16.20.

The columns on the right, plotted on a vertical scale only one fifth of that used for the columns on the left, contrast the basophilic degeneration index in the group of miscellaneous control cases (17) with that in the cases of atrophy of the thyroid gland (18). The numerals at the base of each column correspond to the numbers in the first column of table 2. Again to conserve space, the basophilic degeneration index for group 18 is represented as two columns which may be superimposed on each other.

By an accurate quantitative method, group 17 (miscellaneous cases from groups 1 through 13) had a basophilic index of 7.7, and group 18 (cases of atrophy of the thyroid) a basophilic index of 40.5.

OSTEOGENESIS IMPERFECTA

ANATOMIC STUDY OF A CASE

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Osteogenesis imperfecta has been the subject of numerous papers, and the literature includes many case reports with several good descriptions of the gross morphologic changes accompanying the various manifestations of this condition. The cause, however, is still obscure, and the nomenclature used by the various writers shows some confusion. Certain interesting aspects of the case herein described, along with a fairly good history, warrant the addition of this report to the literature.

REPORT OF CASE

This was a coroner's case. The body was received at the department of anatomy in July 1940. The date of death was June 12, 1940. The subject had sold papers from a wheel chair for a number of years. Death was stated to be due to coronary occlusion, and the death certificate gave the age as 55 years. There was no autopsy. No other data were immediately available, but a hospital record discovered a year later gave the subject's age as 29 years in 1923, indicating that the probable age at the time of death was 46 years. The subject appeared to be a large-headed micromelic achondroplastic dwarf. The body had a crown-heel length of 140 cm., and the weight was estimated to be approximately 59 Kg.

A description of the subject taken from the hospital record gives an accurate picture of the body at the time of death, seventeen years later.

"The patient is an achondroplastic dwarf. His occupation is that of a showman. He was admitted to the hospital, April 13, 1923, with a fracture of the right femur. He stated that while getting out of bed he felt a pain in his right hip and was unable to move the limb. He is a poorly developed white man of 29 years. The head is large, and the features are coarse. The frontal region is flattened, and the occiput overhangs the base of the skull. There is a marked bulge of each temporal region. The eyes are deep set, and the lids slant downward at the external canthi. The mouth is straight, and the teeth are poor. The neck and the torso are short and thick. The chest is well developed. The abdomen is normal. The arms are short and stubby. The inferior extremities are short and very crooked. There are tremendous outward bowing of both thighs and anterior angulation of the legs. The patient has not walked for years and stated that at birth he had hydrocephalus and two fractures—one in an arm and one in a leg. At the age of 5 there was a fracture of the hip (thigh?). There have been fourteen fractures in all, including the present fracture of the right femur. Most of the fractures resulted from slipping while he was walking on crutches. Healing requires a long time—about three months. A familial predisposition toward achondroplasia is not indicated. The parents are dead. One brother (living and well) is well developed. There is no history of venereal disease, but the patient has had measles, scarlet fever, influenza, pneumonia and pleurisy.

"The diagnosis is achondroplasia and fracture of the right femur.

"April 27, 1923, roentgen examination of the inferior right extremity showed marked deformity of the bones of the thigh and the lower part of the leg, and considerable loss of lime salts in all parts of the bony structures. Some new bone formation was shown about both the concave and the convex borders of the bones of the thigh and the lower part of the leg. A pathologic fracture was present in the shaft of the femur about 2 inches (5 cm.) below the lesser trochanter—the two fragments nearly forming a right angle. These findings are rather suggestive of osteomalacia.

"May 8, 1923 roentgen examination showed the presence of a transverse fracture in the proximal portion of the shaft of the femur, with upper displacement of the superior fragment. There was considerable overriding, and the two fragments formed a right angle. The femur was in the position of coxa vara. No definite callus formation could be seen.

From the Department of Anatomy of the University of Cincinnati College of Medicine.

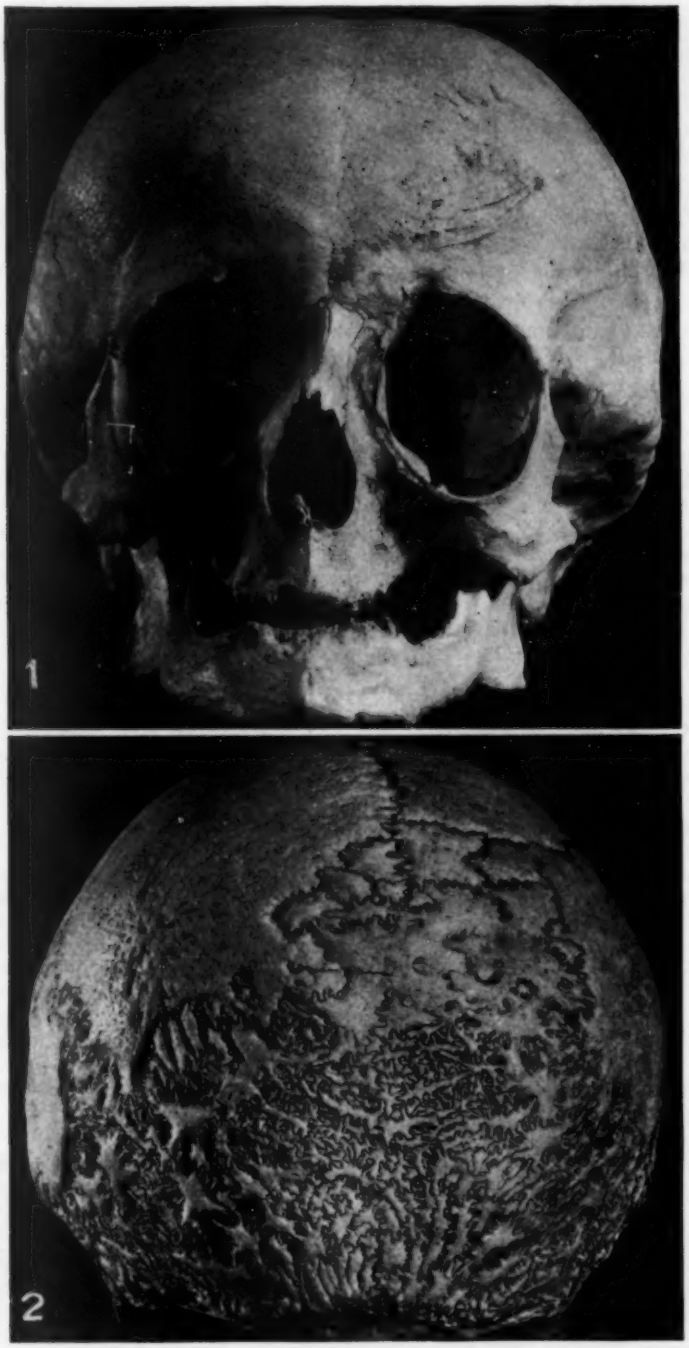
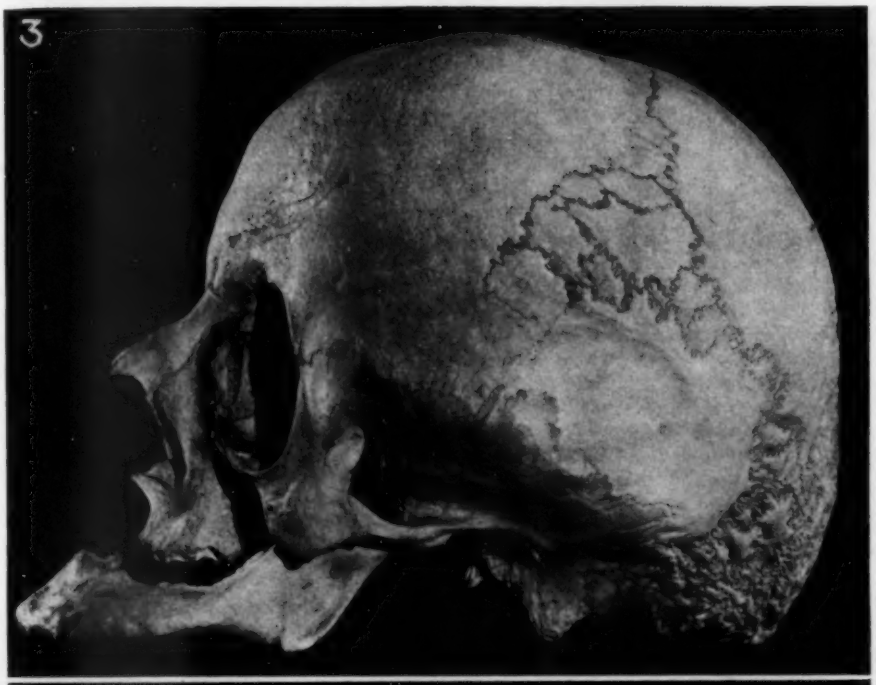


Fig. 1.—Frontal aspect, showing the large oblique slanting orbits, the reduced size of the maxillas and the lateral bulge of each temporal region.

Fig. 2.—Occipital aspect, showing the mosaic of wormian bones.



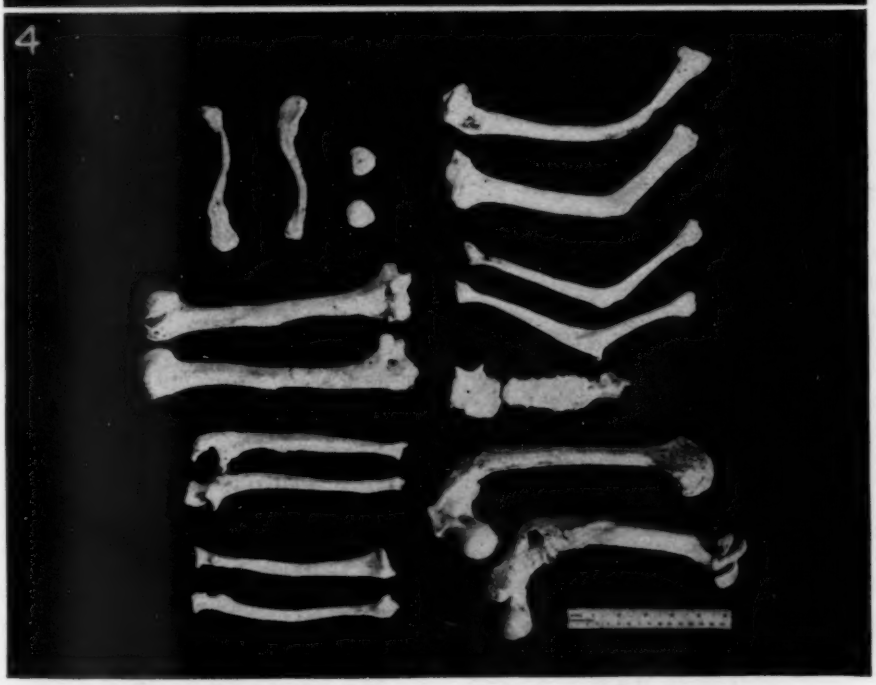


Fig. 3.—Lateral aspect, showing the temporal bulge, the laterally compressed mastoid process and the healed fracture of the left nasal bone.

Fig. 4.—Sternum, clavicles and some of the appendicular bones, showing relative size, bowing and angulation. The femurs, tibias and fibulas exhibit most profound changes.

"The patient was discharged, unimproved, after forty days of hospitalization. He felt well and had no fever, but there was no bony union whatever."

Postmortem observations made during the "roughing out" of the skeleton were not detailed, but reflection of the scalp over the occipital region disclosed an extensive subgaleal hematoma over a transverse fracture across the obelion. The squamous part of the occipital bone above the superior nuchal line and some parts of the parietal bones were observed to be replaced by a mosaic of wormian bones. More limited hemorrhage was found over two fracture lines radiating from the foramen magnum. Further "roughing out" revealed the peculiar morphologic changes and the presence of healed multiple fractures of the bones of the extremities.

The skeleton as a whole was small and relatively light, weighing 2,326 Gm. All of the bones were smaller and weighed less than the same average adult bones. The dwarfism was due to actual bowing of bones, great angulation of improperly healed fractures and the degree of micromelia present.

The structural abnormalities of the vertebral column were confined to absence of the spine of the eleventh thoracic vertebra and abnormal anterior compression of the bodies of the twelfth thoracic and second sacral vertebrae. The lower sacral vertebrae were bent at almost a right angle with the upper two. There were six sacral segments. All of the vertebrae were unusually small.

A peculiar ragged and punched-out appearance of the ribs in the region of the costochondral joints was apparently due to irregular ossification of the costal cartilages for several centimeters beyond the distal ends of the shafts. There was a healed fracture of one rib, with a large amount of callus present.

The bones of the upper extremities showed no marked deformities but were relatively small and light in weight. The deltoid tuberosities were unusually prominent. The left humerus was bowed medially in its distal third. There was some medial bowing of both the radiuses and the ulnas.

The innominate bones were small but normal in shape. The hip bone index $\frac{\text{iliac breadth} \times 100}{\text{ischioiliac height}}$ was 70.94, while the usual hip bone index in man ranges from 74 to 90 (Jamieson [1]). The bones of each thigh and of the lower part of each leg showed profound morphologic changes as a result of multiple fractures. The femurs were bent at the site of several healed fractures at the approximate junction of the upper and middle thirds of their shafts. The angle of the neck with the shaft in the right femur was 97 degrees, while the same angle in the left femur was 40 degrees. The normal angle is 125 degrees. The shafts were twisted so that the patellar surfaces faced laterally and the knee joints functioned on an anteroposterior axis instead of the usual transverse axis.

The fracture of the right femur (discussed in the hospital record) subsequently healed, with the two fragments remaining at approximately a right angle (fig. 4). A bony end to side ankylosis united the two. Osteophytes that formed between the lesser trochanter and the medial side of the lower fragment gave the surface of the bone a jagged and irregular appearance. Two open transverse channels passed through the point of union of the fragments. The free end of the upper fragment had been rounded off, and there was no continuity between the medullary cavities of the two.

The tibias and the fibulas were bent anteromedially and showed an extreme degree of lateral compression. The bones of the ankles and the feet were smaller than average, and the metatarsals were disproportionately narrow through the shafts.

The cranium was large, and its appearance immediately suggested hydrocephalus. The bones of the calvarium were thin, varying from 3 mm. in thickness in the temporal regions to 6 mm. in the frontal and occipital regions. The face was small, and the cranial vault was high (fig. 1). A median depression between the large frontal eminences extended from the nasion to the bregma and contained the partially obliterated metopic suture. The obliquely placed orbits were large and slanted laterally. The small receding maxillary bones accentuated the large size of the orbits. Twelve irregular snags of teeth remained—five in the mandible and seven in the maxillas. The mandible was prognathous, and the genial tubercles appeared as foliate processes extending 1 cm. backward from the mental symphysis. The mandibular ramus was low, and there was considerable erosion of the articular surfaces of the condyloid processes. The nasal bones and septum were deflected to the right, but there was no depression of the bridge of the nose. A healed fracture was present at the junction of the distal and middle thirds of both nasal bones.

1. Cunningham, D. J.: Textbook of Anatomy, edited by E. B. Jamieson, ed. 7, New York. Oxford University Press, 1937, p. 312.

Each temporal region had a pronounced lateral bulge, and the squamous part of each temporal bone appeared to be formed from several superimposed layers of bone (fig. 3). The occipital region extended backward beyond a normal contour, and the external occipital protuberance was depressed below the level of the foramen magnum. Three large interparietal bones across the vertex and behind the coronal suture gave an asymmetric appearance to the vertex of the calvarium and to the sutural pattern.

The most remarkable aspect of the skull was the large number of wormian bones present. Each suture of the calvarium had a number of these bones, while parts of the parietal bones and all of the squamous part of the occipital bone above the external occipital protuberance were replaced by a mosaic of wormian bones (fig. 2). These bones were largest along the posterior border of the coronal suture, where one was 7 cm. long and 5.5 cm. wide. They became smaller over the parietal and occipital regions—some of them being mere bony spicules less than 1 mm. in length or width. Over one hundred large and medium-sized bones could be counted, but the small ones were so complex in their interlocking processes that they could not be counted accurately.

Examination of the internal features of the cranium revealed unusually wide and shallow middle and posterior cranial fossae. The dorsum sellae turcicae slanted forward at an unusual angle so that its posterior surface was in a straight line with the clivus (occipitosphenoidal slope). The endocranial outlines of the wormian bones corresponded fairly closely with the ectocranial pattern, but it was apparent that some of the internal outlines represented more than one of those seen externally in the same area.

Roentgenograms of the skeleton showed most of the characteristics associated with osteogenesis imperfecta: loss of lime salts; irregular medullary cavities and thinning of the cortex in the long bones; multiple fractures; angulation of the bones from improperly treated fractures; excessive callus formation in several locations, and actual bowing of the bone in the absence of fractures (bones of the superior extremities).

The medullary spaces of the shafts of the long bones showed great variation in width from an almost normal appearance in the humeri to a constriction that approached complete obliteration in the middle of the shafts of the bones of the forearms, thighs and lower parts of the legs. The most marked narrowing was seen at the sites of fractures where there was definite angulation.

Lines of retarded growth (Harris [2]) appeared in the metaphyses of most of the long bones. The radiuses, the ulnas and the fibulas showed considerable subperiosteal bone formation especially at the sites of fractures or of bowing of the bones.

COMMENT

Most of the conditions usually considered pathognomonic of osteogenesis imperfecta are seen in this case. Blue scleras were not mentioned in the hospital record, and at autopsy the eyes were too desiccated and discolored to permit determination of the color of the scleras.

Hektoen [3] described a body that was morphologically similar to the present subject except that the whole skeleton was smaller. He gave a detailed account of the skeletal changes and expressed the belief that the condition was osteogenesis imperfecta. Multiple wormian bones and other changes in the skull along with bowing of the long bones and multiple fractures were the basis of the diagnosis, although certain characteristics of the skeleton and the associated dwarfism suggested achondroplasia. Armstrong [4] described a "many boned" skull that was characterized by multiple wormian bones and several other structural anomalies and deficiencies that made him believe that he was dealing with osteogenesis imperfecta. Chont [5] reported 12 cases and reviewed the more important literature. He did not believe that Hektoen's subject had osteogenesis imperfecta.

The skull of the subject herein described had many of the structural abnormalities discussed in the cases of Hektoen, Armstrong and others. However, it is

2. Harris, H. A.: Arch. Int. Med. **28**:785, 1926.
3. Hektoen, L.: Am. J. M. Sc. **125**:751, 1903.
4. Armstrong, A. B.: Anat. Rec. **38**:97, 1928.
5. Chont, L. K.: Am. J. Roentgenol. **45**:850, 1941.

well known that multiple wormian bones and other morphologic variations may be found in several of the cranial dysostoses and alone cannot be considered pathognomonic of any of them. Stieda [6] associated numerous wormian bones with hydrocephalus. Others have mentioned this structural variation in cleidocranial dysostosis and osteogenesis imperfecta. Additional characteristics which establish the diagnosis in this case are seen in the history (fractures at birth; multiple fractures from trivial traumas, with or without bowing or angulation) and in the roentgenograms of the skeleton (rarefaction and thinning of the cortex irregularity of the medullary spaces of the long bones).

The lateral bulge of the temporal region has been described by other authors (Ostheimer; [7] Wagoner [8]), but the long time required for the healing of fractures in this case is atypical as rapid repair has been observed clinically in most of the cases reported.

In several of the cases recorded in the literature the osteogenesis imperfecta was associated with dwarfism. The relation between osteogenesis imperfecta and dwarfism is not explained. In some cases the dwarfism was more apparent than real, being due to shortening of the limbs by angulation and bowing of the bones. In others definite micromelia was present with corresponding diminution in size of all skeletal parts. Many of the dwarfs were reported to have large heads, suggesting hydrocephalus occurring at some time in early life.

SUMMARY

A description is given of the skeleton of a micromelic dwarf with osteogenesis imperfecta. Multiple fractures with bowing and angulation of the bones of the inferior extremities account for a certain degree of dwarfism, but all of the bones of the skeleton were diminished in size, so that the subject was a real dwarf. Developmental defects, including numerous wormian bones, account for the peculiarities seen in the skull. Roentgen findings include rarefaction of the cortex and irregular medullary cavities of the long bones, with numerous lines of retarded growth at the metaphyses. The history cites birth fractures and multiple fractures from trivial traumas up to the age of 29 years as further evidence in support of the diagnosis.

6. Stieda, H.: Anat. Hefte **2**:59, 1892.
7. Ostheimer, M.: J. A. M. A. **63**:1996, 1914.
8. Wagoner, G. W.: Ann. Surg. **80**:115, 1924.

General Reviews

PATHOLOGY OF THE PANCREATIC ISLETS

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Mounting interest in the pathology of the pancreatic islets is due mainly to three factors: (1) the discovery of the relationships between the anterior lobe of the pituitary gland and the islet system, together with the possibility of producing experimental diabetes in an endocrine way, (2) the establishment of the distinct clinical entity of hypoglycemia and (3) the improved histologic technic which permits clearer differentiation between cell types.

The purpose of this paper is to give a comprehensive picture of present knowledge in this field without attempting to present an exhaustive survey of all data available. For more detailed information the reader will be referred to other reviews on the various aspects of the problem.

NORMAL HISTOLOGY OF THE PANCREATIC ISLETS

Appearance and Structure of the Component Cells.—The insular system consists of cells (islet cells) distributed irregularly among the pancreatic acini and possessing a characteristic appearance and structure. Their shape is polygonal or cuboidal, sometimes columnar or wedgelike. Although in certain species their nuclei have a typical chromatin structure, in man the nuclei of the islet cells do not differ markedly from those of the acinous cells. With most routine stains their cytoplasm is homogeneous and much lighter than that of the acinous cells because of the absence of both zymogen granules and chromidial substance. The Golgi net in the islet cell is much more delicate than that in the acinous cell. The mitochondria are small, almost dustlike, much like those of the duct cells, differing markedly from the rather bulky filamentous mitochondria of the acinous cells. The most distinctive property of the islet cells, however, is their granulation, demonstrable only with special stains. These granules set them off sharply from both acinous and duct cells, which do not contain such granules.

Islet cells form well circumscribed, more or less bulky solid groups of a rather typical structure (the islets) but are also found scattered singly or in poorly delimited small groups among the acinous cells and in the lining of small ducts.

Number and Size of the Islets.—The islets can be studied as to number and size either by the supravital staining methods devised by Bensley,[1] which permit counts on whole pancreases of small animals, or by counting and measuring the islets in histologic sections taken from different portions of the gland. The latter point is of considerable importance as the distribution of the islets may vary considerably in different portions of the gland. It has been assumed that islets are more numerous in the tail of the gland than elsewhere, although Clark[2] did not find much difference between islet counts in the duodenal portion and the tail.

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1. Bensley, R. R.: Am. J. Anat. **12**:297, 1911.
2. Clark, E.: Anat. Anz. **43**:81, 1913.

Heiberg [3] counted the islets in the splenic end and found that they may number from 50 to over 150 in an area of 50 sq. mm. Clark,[2] using the supravital perfusion method, counted 208,000 to 1,760,000 islets in the human pancreas. Ogilvie,[4] by the planimetric method, found 100,000 to 500,000 islets in the pancreas of the newborn, while in adults the range was from 230,000 to 2,300,000, most cases being around 500,000. He also calculated the total weight of the islets and gives it as ± 0.1 Gm. in children and 0.5 to 2.3 Gm. in adults. Chiovenda [5] determined the total volume of the islets and found that it ranged from 490 to 1,000 cu. mm. Susman [6] expressed the area of the islets in percentages of the total pancreatic area: In normal adults the limits are 0.9 and 2.7 per cent; in infants, 0.9 and 3.6 per cent. It seems that total area and total volume of islets, expressed either in absolute terms or in percentages, are more meaningful than a simple count because, as Fumagalli [7] pointed out, many of the islets have an irregular shape and one islet may be included several times in the same section.

In size the individual islets may range from a single cell to a group 300 microns in diameter; occasionally even larger islets can be found under perfectly normal conditions. The average diameter of the islets is between 75 and 150 microns (Warren [8]).

A few data concerning experimental animals are available. The number of islets in the pancreas of the guinea pig is from 15,000 to 56,000, according to Bensley.[1] Richardson and Young [9] found that the islets occupy 1 to 1.5 per cent of the total area in sections of pancreases from Wistar rats, whereas the area of the islets in Norwegian hooded rats is as high as 4.5 per cent, a figure that in the case of Wistar rats would be distinctly pathologic.

In the face of these tremendous individual variations the utmost care should be exercised before statements are made as to increase or decrease in the number or in the size of the islets in a particular case or under certain experimental conditions.

Structure of the Islets.—The islets are composed of anastomosing short cords, usually only one or two cells thick, and, especially in the larger ones, of small solid groups of cells. The cords are separated by thin-walled capillaries, which are the only connective tissue in many islets, although reticulum fibers may effect a certain amount of lobulation. The islets are delimited more or less completely against the surrounding acinous parenchyma by the basement membranes of acini and ducts or by the interacinous connective tissue. They do not have a capsule in the strict sense of the word and may be in direct contact with acini, without any intervening connective tissue (Otani [10]). Some islets are in direct continuity with ducts. A special kind of islets are the neuroinsular complexes, first described by van Campenhout [11] and extensively studied by Simard.[12] They seem to be constant organites in the pancreases of all species (Simard [12]; Wilhelm [13]). They are composed of islets in intimate contact with sympathetic ganglion cells. Nothing is known about

3. Heiberg, K. A.: Virchows Arch. f. path. Anat. **204**:175, 1911.
4. Ogilvie, R. F.: Quart. J. Med. **30**:287, 1937.
5. Chiovenda, M.: Arch. ital. di anat. e istol. pat. **11**:95, 1939.
6. Susman, W.: J. Clin. Endocrinol. **2**:97, 1942.
7. Fumagalli, Z.: Arch. ital. di anat. e istol. pat. **11**:326, 1940.
8. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1938.
9. Richardson, K. C., and Young, F. G.: J. Physiol. **91**:352, 1937.
10. Otani, S.: Am. J. Path. **3**:1, 1927.
11. van Campenhout, E.: Arch. de biol., Paris **35**:45, 1925; **37**:121, 1927.
12. Simard, L. C.: (*a*) Arch. d'anat. micr. **33**:49, 1937; (*b*) Rev. Canad. de biol. **1**:1, 1942.
13. Wilhelm, F.: Zentralbl. f. inn. Med. **61**:693, 1940.

their functional significance; Simard expressed the belief that they may be chemoreceptors concerned with the regulation of the secretion of insulin.

Extrainsular Islet Cells.—The occurrence of typical islet cells outside of the cell collections recognizable as islets has been mentioned by several authors (Baumann[14]; Gomori[15]; Simard[12b]). Some may be found scattered among the acini; the cross sections thus interpreted might represent slender peripheral processes of larger islets, rather than single cells outside of all insular relationship, wedged in between acinous cells. Others are embedded in the lining of ducts. They are likely to be completely missed if only routine stains are used but can be discovered easily in thin sections stained for specific granules. In certain animal species, such as the white whale, extrainsular islet cells are numerous. Unfortunately, quantitative data as to their occurrence under normal and under pathologic conditions are not available, although such data would be of great interest. A high count of extrainsular islet cells would explain such puzzling cases as that of Binger and Keith[16] in which no islets could be found in the pancreas at autopsy although there was no evidence of diabetes in vivo.

Acinus-Islet Relationship.—The relation between the islets and the acini has been a moot point practically ever since the discovery of the islets. The formation of both the acini and the islets from the ducts is admitted by all students of the problem. However, opinions are divided on the fixity of the two tissue types once fully differentiated. One group of workers[17] found no evidence for acinoinsular transformation and assert that both acini and islets are specific, noninterchangeable tissues which are capable of further growth or regeneration by the division of their own cells, besides by new formation from ducts. Another, equally numerous group[18] have maintained that the relation between islets and acini is dynamic rather than static and that conversion of acini into islets and vice versa does occur under functional stimuli even in the adult organism.

This divergence of opinions is due mainly to the application of too lax criteria to the diagnosis of acinoinsular transformation. Since at times it may be quite difficult to decide on the basis of routinely stained slides whether a particular cell is an acinous or an islet cell, the subjective factor will become of decisive importance

14. Baumann, A.: Ztschr. f. mikr.-anat. Forsch. **46**:223, 1939.

15. Gomori, G.: Am. J. Path. **17**:395, 1941.

16. Binger, M. W., and Keith, N. M.: J. A. M. A. **109**:1, 1937.

17. (*a*) Kyrle, J.: Arch. f. mikr. Anat. **72**:141, 1908. (*b*) Homans, J.: Proc. Roy. Soc., London, s.B **86**:73, 1912. (*c*) Löwenfeld, W., and Jaffé, R. H.: Virchows Arch. f. path. Anat. **216**:10, 1914. (*d*) Jackson, F. S.: J. Metab. Research **2**:141, 1922. (*e*) Bowie, J. D.: Anat. Rec. **29**:57, 1924. (*f*) Abruzzese, G.: Pathologica **18**:121, 1926. (*g*) Ukai, S.: Mitt. ü. allg. Path. u. path. Anat. **3**:173, 1927. (*h*) Neubert, K.: Arch. f. Entwcklngsmechn. d. Organ. **111**:29, 1927. (*i*) Liegner, B.: Ztschr. f. mikr.-anat. Forsch. **30**:494, 1932. (*j*) Rathery, F., and Touriaf, J.: Compt. rend. Soc. de biol. **128**:155, 1938. (*k*) Bensley.[1] (*l*) Gomori.[15]

18. (*a*) Vincent, S., and Thompson, F. D.: Internat. Ztschr. f. Anat. u. Physiol. **24**:61, 1907. (*b*) Laguesse, E.: J. de physiol. et path. gén. **13**:5, 1911. (*c*) Fischer, H.: Arch. f. mikr. Anat. **79**:276, 1912. (*d*) Koch, K.: Virchows Arch. f. path. Anat. **211**:321, 1913. (*e*) Saguchi, S.: Am. J. Anat. **28**:1, 1920. (*f*) Ogata, S.; Kawakita, H., and Oka, H.: Tr. Jap. Path. Soc. **10**:98, 1920. (*g*) Miyairi, S.: Proc. Imp. Acad. Japan **3**:702, 1927. (*h*) Kolossow, N. G.: Ztschr. f. mikr.-anat. Forsch. **11**:43, 1927. (*i*) Collin, R.; Drouet, P. L.; Watrin, J., and Florentin, P.: Compt. rend. Soc. de biol. **108**:64, 1931; (*j*) Rev. franç. d'endocrinol. **10**:271, 1932. (*k*) Florentin, P.; Picard, D., and Weis, M.: Compt. rend. Soc. de biol. **117**:188, 1934. (*l*) Picard, D.: ibid. **120**:153, 1935. (*m*) Florentin, P., and Picard, D.: Rev. franç. d'endocrinol. **14**:1, 1936. (*n*) Tusques, J.: Compt. rend. Soc. de biol. **129**:1103, 1938. (*o*) Woerner, C. A.: Anat. Rec. **71**:33, 1938. (*p*) Aubertin, E.; Lacoste, A., and Saric, R.: Ann. de méd. **43**:253, 1938. (*q*) Hoffmann, E.: Ztschr. f. d. ges. exper. Med. **104**:721, 1939. (*r*) Sergeyeva, M. A.: Anat. Rec. **77**:297, 1940. (*s*) Simard.[12b]

in settling the question. This is especially true in cases of regeneration and hypertrophy of the islets when the acinoinsular boundary may become more or less jumbled (Collin and co-workers [18i, j]; Florentin and co-workers [18k]; Picard [18l]; Aubertin and co-workers [18p]). These changes in structure, however, can be explained by the peculiar blood supply of the pancreas (Wharton [19]), which permits the spread of insular hyperemia to the surrounding acini. Since the one positive means of identification of both acinous and islet cells is the demonstration of their specific granules, the only cogent evidence for acinoinsular transformation would be the finding, with specific stains, of cells containing both types of granules (Bensley [1]). If this criterion is accepted, the overwhelming majority of papers championing acinoinsular transformation must be dismissed because their thesis is supported by insufficient evidence. In some of these papers the conclusion is based on speculation rather than on sound morphologic evidence (H. Fischer [18c] Laguesse [18b]; Ogata and associates [18f]; Vincent [20]). Others take the lack of complete delimitation of the islets against the acini by a connective tissue capsule, the apparent continuity of the two tissues in many places, as an evidence of transition (Koch [18d]; Collin and co-workers [18i, j]; Florentin and co-workers [18k]; Picard [18l]; Aubertin and co-workers [18p]; Hoffmann [18q]), although, as Neubert [17h] remarked, this continuity should be interpreted only as a survival of embryonic connections.

Picard claimed to have observed all stages of the formations of islet cells from acinous cells—a very peculiar process which he called endocytogenesis. It consisted of the formation of a daughter cell within the acinous cell and the extrusion of this endocyte as a full-fledged islet cell. Although the illustrations given in his paper are striking, the evidence is not conclusive because specific stains were not used.

Another cause of confusion is the presence of so-called Mankowski [21] cells. They are probably degeneration products of acinous cells (Bensley [1]) and can be observed under a variety of conditions. The typical Mankowski cell contains acidophilic granules much finer than zymogen but coarser and less uniform than alpha granules. With most stains, including neutral stains of the Lane-Bensley type, they stain like alpha granules. However, certain staining methods permit their differentiation from alpha cells (Gomori [15]). The Mankowski cells seem to have misled a number of investigators into the belief that they had witnessed the transformation of acinous cells into islet cells (S. Vincent [20]; Kolossow [18h]; Pickard [18l]; Sergeyeva [18r]).

In the literature reviewed there are only two reports of the finding of cells containing both zymogen and islet granules based on technically unobjectionable observations (Woerner [18o]; Simard [12b]). They should be checked by other investigators.

Cell Types.—The first observations on the presence of more than one type of cell in the pancreatic islets date back almost fifty years (Laguesse [22]; Diamare [23]; Schulze [24]). The foundations of the morphology and the knowledge of the staining properties of the islet cells were laid by Lane [25] and Bensley [1] in 1907 and 1911, respectively. Lane distinguished two cell types in the islet of the guinea pig: the

19. Wharton, G. K.: Anat. Rec. **53**:55, 1932.
20. Vincent, S.: Lancet **1**:947, 1924.
21. Mankowski, A.: Arch. f. mikr. Anat. **59**:286, 1902.
22. Laguesse, E.: Compt. rend. Soc. de biol. **10**:667, 1894.
23. Diamare, V.: Internat. Monatschr. f. Anat. **16**:155, 1899.
24. Schulze, W.: Arch. f. mikr. Anat. **56**:491, 1900.
25. Lane, M. A.: Am. J. Anat. **7**:409, 1907.

A cells, containing granules preserved by alcohol and dissolved by aqueous potassium dichromate–mercury bichloride solution, and beta cells, whose granules are preserved by aqueous and dissolved by alcohol. To these types Bensley added a third, a non-granular variety. For staining Lane used a compound dye obtained by precipitating gentian violet with orange G ("neutral gentian"). The preserved granules are stained blue. This distinction of two cell types together with the nomenclature (with Latin and Greek letters used promiscuously) was subsequently universally accepted, although some of the statements of Lane regarding the solubility of the granules were later disproved. For instance, from the fact that alpha granules fail to stain with neutral gentian after being fixed with aqueous potassium dichromate–mercury bichloride solution Lane drew the conclusion that they are dissolved by this fixative. Subsequently, many investigators [26] obtained good visualization of the alpha granules after using this fixative and similar ones. Lane asserted also that trinitrophenol or acetic acid will do away with all islet granules, although fixatives containing these acids were subsequently used by a number of workers [27] with excellent results. However, the fact remains that the two cell types were first defined by Lane in terms of their staining reactions. This definition should be adhered to until a better one is found, and the results of all new methods should be compared with those of the original Lane technic before any statements as to specificity are made.

On the analogy of Lane's neutral gentian stain a number of similar "neutral" stains were developed (Martin [28]; Bowie [17e]; Bayley [26e]), of which Bowie's ethyl violet–Biebrich scarlet seems to have gained considerable popularity.

The neutral stains have several serious drawbacks. The results are greatly influenced by moderate changes in the concentration of hydrogen ions in the fixative. The addition of 2 per cent acetic acid completely reverses the effect in that now the alpha cells stain with the basic component and the beta cells with the acid one. All intermediate shades are possible with slight variations in the acidity of the fixative. This reversibility of color effect is responsible for some confusion in the identification of the cell types. Warren [29] stated that after fixation in Zenker solution alpha granules cannot be demonstrated. Sergeyeva,[30] using the identical technic in two different series of experiments, called the cells showing blue granules beta in one of her reports and alpha in the other one. The shades also depend on the degree of differentiation in the alcohol–oil of clove mixture. But even though the instructions are followed with meticulous care the results are far from being uniform. Even in guinea pig material, to which the neutral stains were originally applied, the results are rather capricious, especially under pathologic conditions (Kirkbride [26a]; Milne and Peters [31]; Hinteregger [32]; Vincent [20]; Arndt and Neumann [33]; Gomori [27a]). In other species the results are usually poor, often entirely

26. (*a*) Kirkbride, M. B.: J. Exper. Med. **15**:101, 1912. (*b*) Martin, W. B.: J. Metab. Research **1**:43, 1922. (*c*) Miyairi, S.: Tr. Jap. Path. Soc. **16**:89, 1926. (*d*) Bloom, W.: Anat. Rec. **49**:363, 1931. (*e*) Bayley, J. H.: J. Path. & Bact. **44**:272, 1937. (*f*) Gomori, G.: Am. J. Path. **15**:497, 1939. (*g*) Ukai.[17g] (*h*) Woerner.[18o] (*i*) Sergeyeva.[18r]

27. (*a*) Gomori, G.: Anat. Rec. **74**:439, 1939. (*b*) Hartz, P. H.: Arch. Path. **33**:541, 1942. (*c*) Martin.[26b] (*d*) Bowie.[17e] (*e*) Simard.[12b]

28. Martin, W. B.: Anat. Rec. **9**:475, 1915.

29. Warren, S.: Am. J. Path. **2**:335, 1926.

30. Sergeyeva, M. A.: Anat. Rec. **71**:319, 1938. Sergeyeva.[18r]

31. Milne, L. S., and Peters, H. L.: J. M. Research **26**:405, 1912.

32. Hinteregger, F.: Beitr. z. path. Anat. u. z. allg. Path. **87**:555, 1931.

33. Arndt, H. J., and Neumann, H. O., in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1933, vol. 8, pt. 1, p. 1700.

unusable (Homans [17b]; Herring [34]; Herxheimer and Carpentier [35]; Meyenburg [36]; Schmid [37]; Gomori [27a]; Laidlaw [38]; Ham and Haist [39]). The failure to obtain clearcut differentiation with the neutral stains led Herxheimer and Carpentier to disbelieve altogether in the existence of two different cell types.

The Mallory-Heidenhain azan stain, first suggested by Bloom [26d] for this purpose, is extremely valuable for the study of islet cells. It gives brilliant results after practically all aqueous fixatives and in all animal species, including man (Thomas [40]; Nagelschmidt [41]; Gomori [27a]). It is hard to explain how Neubert,[17h] who used it four years before Bloom, failed to obtain the same results, the more so as his material seems to have been fresh. In most species the azan stain demonstrates three different cell types; the alpha cells contain ruby red granules, the beta cells somewhat indistinct orange-gray granules, and a third variety (D), unrecognizable with the neutral stains, sky blue ones. The only species in which the staining reactions of the alpha and beta cells are reversed is the guinea pig (Gomori [27a]). The color contrasts can be enhanced by a slight modification of the technic. The only shortcoming of the azan stain is its failure to give a sharp picture of the important beta granules.

The original Mallory acid fuchsin–aniline blue–orange G stain and some of its modifications (Ukai [42]; Warren [8]) will also differentiate between alpha and beta cells, but the results are inferior to those of the azan stain.

The chromium hematoxylin–phloxine stain described and later slightly modified by Gomori [43] can be used after practically any aqueous fixative and in all of the common animal species. It works well even on not entirely fresh material. Alpha cells show red and beta cells blue granules; the pictures are sharp. D cells are indistinguishable from alpha cells.

Richardson [44] combines the iron-hematoxylin stain with Mallory's phosphotungstic acid–hematoxylin stain. The beta granules are stained pale gray; the alpha granules, blue-black. In human material the results with this method were found to be unsatisfactory.

Two more stains deserve mention because of the clarity of the pictures they give. The first one is Mallory's phosphotungstic acid–hematoxylin, especially as modified by Gomori.[15] It stains alpha granules steel blue and is useful in distinguishing alpha cells from Mankowski cells. The second one is silver impregnation either in frozen sections according to the Gros-Schulze method (Nagelschmidt [41]) or in paraffin sections according to the Rogers technic (Simard [12b]).

Hartz [27b] suggests a modification of Masson's tetrachrome stain as a routine technic for islets. However, I have found [45] that with this stain it is the alpha cells which are stained more or less selectively and not the beta cells as Hartz asserts; in fact, the beta cells are poorly differentiated.

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34. Herring, P. T.: Quart. J. Exper. Physiol. **17**:119, 1927.
35. Herxheimer, G., and Carpentier, E.: Beitr. z. path. Anat. u. z. allg. Path. **76**:270, 1927.
36. von Meyenburg, H.: Schweiz. med. Wchnschr. **5**:1121, 1924.
37. Schmid, H. H.: Ztschr. f. Zellforsch. u. mikr. Anat. **26**:146, 1937.
38. Laidlaw, G. F.: Am. J. Path. **14**:125, 1938.
39. Ham, A. W., and Haist, R. E.: Am. J. Path. **17**:787, 1941.
40. Thomas, T. B.: Am. J. Anat. **62**:31, 1937.
41. Nagelschmidt, L.: Ztschr. f. mikr.-anat. Forsch. **45**:200, 1939.
42. Ukai, S.: Mitt. ü. allg. Path. u. path. Anat. **3**:1, 1927.
43. Gomori.[27a] Gomori.[15]
44. Richardson, K. C.: Proc. Roy. Soc., London, s.B **128**:153, 1940.
45. Gomori, G.: Unpublished data.

In summarizing the survey of the staining technics it may be said that the neutral stains are not dependable for the identification of cell types but may be useful in the study of degranulation processes. The chromiumhematoxylin–phloxine stain gives a clear picture of the two main cell types, while for the identification of the D cells the Mallory-Heidenhain stain is indispensable. Complete information on the islets from the standpoint of cytology can be obtained by staining sections with these two stains. The results are strictly comparable since there is no overlapping of cell types identified by these methods (Gomori [15]).

A large number of species were studied with the stains mentioned, and it was found that the islets of practically all of them contain alpha, beta and D cells (Thomas [40]; Gomori [27a]; Simard [12b]). In some species the presence of D cells cannot be established beyond doubt (Gomori). In two species, the teleost Neomaenis griseus (Bowie [17e]) and the opossum, additional cell types have been demonstrated. The five cell types found by Saguchi [18e] in the pancreas of the frog are based on entirely different cytologic criteria; they cannot be compared with the cell types mentioned. Besides the granulated cell types mentioned, agranular cells have been found in several species. Whether these cells represent a type *sui generis* or just degranulated specimens of the other three types is an open question.

In the islets of some species the different cell types are intermingled without any recognizable pattern (guinea pig, dog); in those of other species they tend to cluster together in a characteristic way. For instance, in the rat the alpha cells occupy the periphery of the islet, while in the horse and in the cat they occupy the center. In human islets the alpha cells show a tendency to nestle against capillaries, while the beta cells occupy the more avascular areas (Gomori [15]). The pancreases of birds show two different types of islets; the so-called dark islets consist exclusively or predominantly of alpha and D cells, the light islets mainly of beta cells (Nagelschmidt [41]; Miller [46]).

In most species the beta greatly outnumber the alpha cells (Simard [12b]). Actual counts are available only on human and canine material. According to Gomori,[15] in normal human islets around 60 to 90 per cent of all cells are beta cells, 2 to 8 per cent are D cells and the remainder are alpha cells. Highly vascularized islets have higher alpha cell counts. The extrainsular islet cells in man are mostly alpha cells. In the dog Hunt [47] found the beta : alpha : D ratio to be fixed at 75 : 20 : 5. However, Gomori [15] was unable to confirm the latter datum.

In human islets there is great variability in regard to the extent and the degree to which the cells are granulated. Considerable degranulation, especially of the beta cells, is a common finding even under normal conditions (Gomori [15]). No data are available as to the limits of normal granulation in animals.

Fixity of Cell Types.—This is a much debated question, and again the arguments of some of the investigators are of doubtful value on account of the inadequacy of the staining technics used in their work. This applies especially to the papers of Herxheimer and Carpentier [35] and Hinteregger,[32] who on the basis of admittedly poor results with neutral stains made the statement that they observed intermediate forms between alpha and beta cells. Similar statements by Ohinoue [48] and Florentin and Picard [18m] were based on entirely inadequately stained preparations. Meneghini [49] considered the alpha cells as the resting phase and the beta

46. Miller, R. A.: Endocrinology **31**:535, 1942.
47. Hunt, T. E., abstracted, Anat. Rec. **67**:27, 1937.
48. Ohinoue, T.: Tr. Soc. path. jap. **23**:104, 1933.
49. Meneghini, T.: Ginécologia **5**:539, 1939.

cells as the secretory phase of the same kind of cells. Lane [25] and Bensley,[1] on the other hand, never saw any transitions between alpha and beta cells in their exceptionally well stained preparations. Gomori, using the same chrome-hematoxylin-phloxine stain, also denied the occurrence of such transitions, whereas Simard,[12b] with the same technic, observed cells with both types of granules in the islets of several species. Transitional forms between alpha and D cells were positively identified by Nagelschmidt,[41] Gomori [15] and Miller.[46] Thomas [50] expressed the belief that he had seen cells intermediate between the beta and the D type in the islets of snakes.

RESPONSES OF THE INSULAR TISSUE TO VARIOUS STIMULI

To various acute stimuli, physiologic or experimental, the islets respond as a rule by cytologic changes only. In the case of chronic stimuli, changes in the amount of insular tissue may predominate. The interpretation of some of the results reported is open to doubt, owing to the inadequacy of the staining methods used.

Acute Stimuli.—Homans [17b] reported that under stimulation by secretin the beta cells may become similar to duct cells by loss of granules. Sergeyeva [18r] observed increase in the numbers of alpha cells after adrenergic stimuli and increase in the numbers of beta cells after cholinergic stimuli. A number of data are available on the effects of the administration of dextrose. While Thomas [50] and Gomori and associates [51] reported degranulation of beta cells, Ohinoue [48] found a decrease in the number of alpha cells with a corresponding increase in the beta : alpha ratio; hyperglycemia induced by epinephrine produced the same changes. Poll,[52] with a special method, found homogenization of the cytoplasm of islet cells after injection of dextrose or epinephrine hydrochloride. The acute effect of insulin as reported by Kogan [53] consists in an increase in the number and the size of the islets. Ohinoue found the changes caused by insulin to be similar to those due to hyperglycemia. In the experiment of Sergeyeva [18r] cream feeding caused tremendous enlargement of the islets with a preponderance of alpha cells. Miyairi [18g] studied the effect of dextrose, epinephrine, atropine, pilocarpine and various other drugs on the islets. His descriptions are hard to follow. Recently Shaw Dunn, Sheean and McLetchie [54] made the extremely interesting and important observation that selective necrosis of the islets can be produced in rabbits by certain chemicals.

Chronic Stimuli.—Continued administration of dextrose causes degranulation and vacuolation of islet cells with pyknosis of the nuclei. Kolossow [18h] and Corpaci [55] did not specify the type of cells involved; Woerner [18o] and Ohinoue [48] mentioned explicitly both alpha and beta cells. Moderate doses of sugar administered over longer periods lead to hypertrophy of the islets (Corpaci [55]; Meneghini [49]). Overwhelming amounts of sugar may cause extensive hemorrhagic and edematous changes in the entire gland as shown by Jacobs and Colwell,[56] although under similar conditions Allen [57] noticed no effect.

Reports on the results of prolonged administration of insulin are rather contradictory, probably on account of the widely varying dosages used by different

50. Thomas, T. B.: Anat. Rec. **82**:327, 1942.
51. Gomori, G.; Friedman, N. B., and Caldwell, D. W.: Proc. Soc. Exper. Biol. & Med. **41**:567, 1939.
52. Poll, H.: Verhandl. d. anat. Gesellsch. **39**:179, 1930.
53. Kogan, V.: Ztschr. f. d. ges. exper. Med. **41**:63, 1924.
54. Shaw Dunn, J.; Sheean, H. L., and McLetchie, N. G. B.: Lancet **1**:484, 1943.
55. Corpaci, A.: Sperimentale, Arch. di biol. **86**:129, 1932.
56. Jacobs, H. R., and Colwell, A. R.: Am. J. Physiol. **116**:194, 1936.
57. Allen, F. M.: J. Metab. Research **1**:75, 1922.

authors. A number of writers (Herring [34]; Collin, Drouet, Watrin and Florentin [18i, j]; Aubertin and Mollaret [58]; Aubertin, Lacoste and Saric [18p]; Arpino [59]) have reported hypertrophy and hyperplasia of the islets. Schmid [37] and Miyairi [26c] saw no changes in the amount of islet tissue, while Corpaci found it decreased. Latta and Harvey [60] and Miller [46] found degenerative changes in the beta cells; the latter, also degranulation of the alpha cells. In the experiments of Miyairi the beta cells were poorly granulated, and the alpha cells were almost completely absent. McJunkin and Roberts [61] found that the number of mitoses in islet cells is greatly decreased after continued administration of insulin.

Starvation seems to cause a considerable increase in the amount of islet tissue (Vincent and Thompson [18a]; H. Fischer [18c]; Laguesse [18b]; Vincent [20]; Stefko [62]). Hinterregger,[32] on the other hand, found the islets atrophic and the alpha cells predominant. Labbé and Thaon [63] produced marked hypertrophy and hyperplasia of the islets of the guinea pig by feeding the animals meat.

Pregnancy is accompanied by hyperplastic changes in the islets, according to Rosenloecher,[64] Florentin, Picard and Weis [18k] and Florentin and Picard.[18m] However, Allen [65] failed to notice any change in the pancreases of pregnant bitches.

According to Allen,[65] the sex glands have no appreciable effect on the islets in experimental diabetes. Cramer and Horning [66] found that estrogen causes hypertrophy. Hoffmann,[18q] Tusques [18n] and Rathery and Touriaf [17j] reported definite hyperplasia of the islets in castrated mice and guinea pigs. Habán and Angyal [67] observed no changes in the islets of thyroid-treated animals. Bensley and Woerner [68] observed a number of changes after the intravenous injection of an alpha cell extract; their work, however, is open to criticism because of the questionable purity of their extracts and the lack of controls. Birnkrant [69] obtained degenerative changes in the islets of rats with an extract of salivary glands.

Partial resection of the pancreas invariably, and ligation of the main duct often, cause marked hypertrophy of the islets, the latter procedure usually after initial atrophy (Abruzzese [17f]; Friedman and Marble [70]; Meneghini [71]; Löwenfeld and Jaffé [17c]; Herxheimer [72]; Herxheimer and Carpentier [35]; Alpern and Besuglow [73]; Hüttl [74]; de Takats [75]; Jorns [76]).

Chiovenda [5] found marked increase in the amount of islet tissue in cases of cachexia due to cancer and lymphogranulomatosis.

The effects of anterior pituitary extracts will be discussed under the heading of experimental diabetes.

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58. Aubertin, C., and Mollaret, J.: Compt. rend. Soc. de biol. **110**:383, 1932.
59. Arpino, G.: Folia med. **25**:925, 1939.
60. Latta, J. S., and Harvey, H. T.: Anat. Rec. **82**:28, 1942.
61. McJunkin, F. A., and Roberts, B. D.: Proc. Soc. Exper. Biol. & Med. **29**:893, 1932.
62. Stefko, W. H.: Krankheitsforschung **6**:442, 1928.
63. Labbé, M., and Thaon, P.: Compt. rend. Soc. de biol. **69**:228, 1910.
64. Rosenloecher, K.: Arch. f. Gynäk. **151**:567, 1932.
65. Allen, F. M.: Am. J. Physiol. **54**:451, 1921.
66. Cramer, W., and Horning, E. S.: Lancet **1**:247, 1936.
67. Habán, G., and Angyal, F.: Beitr. z. path. Anat. u. z. allg. Path. **101**:602, 1938.
68. Bensley, S. H., and Woerner, C. A.: Anat. Rec. **72**:419, 1938.
69. Birnkrant, W. B.: J. Lab. & Clin. Med. **27**:510, 1942.
70. Friedman, N. B., and Marble, A.: Endocrinology **29**:577, 1941.
71. Meneghini, T.: Ginecologia **7**:325, 1941.
72. Herxheimer, G.: Klin. Wchnschr. **5**:2299, 1926.
73. Alpern, D. E., and Besuglow, W. P.: Klin. Wchnschr. **7**:586, 1928.
74. Hüttl, T.: Beitr. z. klin. Chir. **163**:206, 1936.
75. de Takats, G.: Arch. Surg. **19**:775, 1929.
76. Jorns, G.: Beitr. z. klin. Chir. **146**:51, 1929.

PATHOLOGIC CHANGES IN THE ISLETS

Natural Diabetes.—The literature on the pathologic changes in the pancreas in diabetes prior to 1938 has been reviewed by Warren.[8] More recent reports have not added new knowledge. Only the main points will be mentioned here.

Clinical diabetes is not necessarily associated with pathologic changes in the pancreas, although the percentage of cases without demonstrable changes varies considerably with different authors (Conroy,[77] none; Gibb and Logan,[78] 7.5 per cent; Cecil,[79] 12 per cent; Meyenburg,[36] 50 per cent). Clinically identical cases may be entirely different from the point of view of pancreatic pathology (Warren[8]). On the other hand, changes described as typical for diabetes are found not too rarely in persons who never had clinical symptoms of the disease (Conroy[77]; Meyenburg[36]; Gomori[15]). This extreme variability of findings, often even in different fields of the same section, is explained by Warren and Root[80] on the basis that the pathologic changes in diabetes represent the results of a long struggle between the diabetogenic injury and the regenerative power of the islets. On the other hand, clinical diabetes will become manifest only when the islets are unable to satisfy the demand for insulin. All gradations between an absolutely incompetent insular system and a normal one that is relatively insufficient only in the face of excessive demand are possible.

The changes usually seen in diabetes will be divided into (*a*) those involving the islets as units and (*b*) those of cytologic nature.

(*a*) Changes in the Islets. These changes are either of degenerative or of regenerative character. Quite often both types are present side by side, but their ratio may vary between extremely wide limits. In most cases the degenerative changes predominate.

The main degenerative changes are a reduction in the amount of islet tissue, fibrosis and hyalinosis (occasionally amyloidosis), lymphatic infiltration, hemorrhage and calcification. As to reduction in the amount of islet tissue, low islet counts in pancreases of diabetics have been reported many times (Heiberg,[3] Conroy,[77] Allen,[81] Warren[82] and others). In the cases of Moore[83] and Gordon[84] no typical islets were observed at all. Warren[8] warned that changes in the number of islets are of no importance unless pronounced. Low islet counts are apparently compatible with normal carbohydrate metabolism; the case of Binger and Keith[16] referred to previously is an extreme example proving this point. Fibrosis and hyalinosis (occasionally amyloidosis) of the islets, with atrophy of the islet cells, are common in natural diabetes of both man and animals (Bloom[85]; Bloom and Handelsman[86]) as well as in experimental diabetes. However, they are seen in nondiabetic persons, too. Lymphocytic infiltration of the islets is mentioned by Cecil,[79] Heiberg,[3] Warren,[82] Meyenburg,[87] Dry and Tessmer[88] and others. Accord-

77. Conroy, M. J.: J. Metab. Research **2**:367, 1922.
78. Gibb, W. F., and Logan, V. W.: Arch. Int. Med. **43**:376, 1929.
79. Cecil, R. L.: J. Exper. Med. **11**:266, 1909.
80. Warren, S., and Root, H. F.: Am. J. Path. **1**:415, 1925.
81. Allen, F. M.: J. Metab. Research **1**:193, 1922.
82. Warren, S.: J. A. M. A. **88**:99, 1927.
83. Moore, R. A.: Am. J. Dis. Child. **52**:627, 1936.
84. Gordon, W. H.: Ohio State M. J. **32**:540, 1936.
85. Bloom, F.: New England J. Med. **217**:395, 1937.
86. Bloom, F., and Handelsman, M. B.: North Am. Vet. **18**:39, 1937.
87. Meyenburg, H. V.: Schweiz. med. Wchnschr. **21**:554, 1940.
88. Dry, T. J., and Tessmer, C. F.: Minnesota Med. **24**:97, 1941.

ing to Warren,[8] it is most likely to be observed in fulminating cases. Hemorrhage (Gibb and Logan [78]) and calcification in the islets (B. Fischer [89]) are rare.

The regenerative changes run a whole gamut of hyperplastic alterations from budding of ducts with the formation of small islet-like cell groups (B. Fischer [89]) through conspicuous enlargement of the islets to diffuse adenomatous hyperplasia (Cecil [79]) and the formation of distinct insular adenoma. A peculiar kind of hyperplasia consisting in the transformation of the islets into tortuous ribbons of columnar cells has been described by MacCallum.[90] The histology of the adenoma seen in diabetes is identical with that of the symptomless or even insulin-producing islet tumors.

(*b*) Cytologic Changes. The typical findings are nuclear pyknosis and hydropic vacuolation of the cells of the islets (Weichselbaum [91]; Allen [81]; Stansfield and Warren [92]; Gibb and Logan [78]; Warren [8]; Meyenburg [87]). They are by no means constant. Vacuolation is most likely to be a prominent feature when the patient dies with intense symptoms (Allen [81]; Warren [8]). That acute strain on the islets may cause vacuolation was suggested by Gomori.[15] He found marked hydropic ballooning of the beta cells in the surgical specimen of a patient who had received large amounts of intravenous dextrose preoperatively. The same changes were seen in 2 similar cases.

Both pyknosis and vacuolation may be closely imitated by postmortem autolysis, from which they have to be differentiated. Small vacuoles may be present in islet cells under normal conditions (Graham and Hartmann [93]; Gomori [15]), but this is entirely different from the hydropic distention of the cells in diabetes.

The cellular composition of the islets in human diabetes has been studied by Gomori.[15] He stated that there seems to be a tendency toward an increase of the alpha : beta ratio, although the differences are of questionable significance. The beta cells, which are preserved even in greatly hyalinized islets, often are remarkably dark, crowded with granules. D cells are present in normal numbers.

A few data are available on the effects of the administration of insulin in human diabetes. Boyd and Robinson [94] found in an insulin-treated child no typical diabetic changes; the islets showed conspicuous signs of hyperplasia, and the beta : alpha ratio was normal. Warren and Root [80] obtained the impression that treatment with insulin protects the islets better than mere dietary management does; similar conclusions can be drawn from the statistical data published by Dry and Tessmer.[88]

(*c*) Pancreatic Changes in Babies Born of Diabetic Mothers. The first report of hyperplastic changes in the islets of a child born of a diabetic mother came from Dubreuil and Anderodias.[95] Subsequently many similar cases were described.[96] Gordon [84] found like hyperplasia of the islets in puppies born of depancreatized bitches.

89. Fischer, B.: Frankfurt. Ztschr. f. Path. **17**:218, 1915.
90. MacCallum, W. G.: Am. J. M. Sc. **133**:432, 1907.
91. Weichselbaum, A.: Wien. klin. Wchnschr. **24**:153, 1911.
92. Stansfield, O. H., and Warren, S.: New England J. Med. **198**:686, 1928.
93. Graham, E. A., and Hartmann, A. F.: Surg., Gynec. & Obst. **59**:474, 1934.
94. Boyd, G. L., and Robinson, W. L.: Am. J. Path. **1**:135, 1925.
95. Dubreuil, G., and Anderodias: Compt. rend. Soc. de biol. **83**:1490, 1920.
96. (*a*) Gray, S. H., and Feemster, L. C.: Arch. Path. **1**:348, 1926. (*b*) Ehrich, W.: Klin. Wchnschr. **13**:584, 1934. (*c*) Gordon, W. H.: J. Michigan M. Soc. **34**:167, 1935. (*d*) Angyal, F.: Centralbl. f. allg. Path. u. path. Anat. **66**:209, 1936. (*e*) Hartmann, A. F., and Jaudon, J. C.: J. Pediat. **11**:1, 1937. (*f*) Rascoff, H.; Beilly, J. S., and Jacobi, M.: Am. J. Dis. Child. **55**:330, 1938. (*g*) Korényi, A.: Gyógyászat **80**:146, 1940. (*h*) Helwig, E. B.: Arch. Int. Med. **65**:221, 1940. (*i*) Potter, E. L.; Seckel, H. P. G., and Stryker, W. A.: Arch. Path. **31**:467, 1941.

The hyperplastic changes are often of a high degree; Gray and Feemster [96a] calculated that in their case the amount of islet tissue present was about twenty-four times the normal. Besides hyperplasia, infiltration of the islets by eosinophil and plasma cells is common.[97] The hyperplastic islets consist mainly of beta cells (Rascoff and co-workers [96f]).

On the basis of the early reports it seemed as if these changes were specific for maternal diabetes. Later, however, Hartmann and Jaudon [96e] and Helwig [96h] found them also in children of normal mothers. Finally, the observations of Potter and associates,[96i] who demonstrated them far more often in the absence than in the presence of maternal diabetes, completely disproved their specific nature.

In this context it is interesting to note that, according to recent observations (Hartmann and Jaudon [96e]; Zondek and Wolfsohn [98]), hypoglycemia in the newborn is a physiologic phenomenon.

Artificial Diabetes.—(*a*) Surgical Diabetes. A condition clinically indistinguishable from human diabetes was produced by Allen [99] in the dog by extensive resection of the pancreas and carbohydrate feeding. At least three fourths of the pancreas had to be resected, but occasionally the removal of as much as eight ninths did not lead to diabetes. Homans [100] resected four fifths or more of the pancreas in cats. Permanent diabetes resulted in but few of these animals.

The first changes in animals made diabetic is the thinning out of the beta granules (Martin [26b]). This is soon followed by increasing vacuolation of the beta cells. The epithelium of small ducts also partakes in the hydropic changes. In extreme stages there is a loss of cells with almost complete disappearance of the islets. The alpha cells remain practically normal throughout.

Copp and Barclay [101] were able to restore to normal the hydropically degenerated islet cells of a dog by means of insulin.

(*b*) Diabetes Induced with Pituitary Extracts. Scattered and disconnected data on the influence of the pituitary gland on the insular system are available from 1908 on. Borchardt [102] reported glycosuria in a large proportion of acromegalic patients, while Goetsch, Cushing and Jacobson [103] found increased carbohydrate tolerance in the later stages of the disease. Kojima [104] produced cytologic changes in the islets of rats by feeding them pituitary gland. Johns, O'Mulvenny, Potts and Laughton [105] observed glycosuria and high blood sugar levels in dogs treated by injections of an anterior pituitary extract. Putnam, Benedict and Teel [106] reported practically no changes in the islets of a dog treated with an extract containing the growth-promoting factor. Baumann and Marine [107] observed glycosuria in rabbits treated with an anterior pituitary extract.

In 1929 and 1930 Houssay and his collaborators [108] published their first reports on the effect of hypophysectomy on diabetes. These extremely important papers

97. Gordon.[84] Gordon.[96c] Rascoff and others.[96f] Korényi.[96g] Helwig.[96h]
98. Zondek, H., and Wolfsohn, G.: Acta med. Scandinav. **106**:468, 1941.
99. Allen, F. M.: J. A. M. A. **63**:939, 1914; J. Exper. Med. **31**:381, 1920.
100. Homans, J.: J. M. Research **30**:49, 1914.
101. Copp, E. F. F., and Barclay, A. J.: J. Metab. Research **4**:445, 1923.
102. Borchardt, L.: Ztschr. f. klin. Med. **66**:332, 1908.
103. Goetsch, E.; Cushing, H., and Jacobson, C.: Bull. Johns Hopkins Hosp. **22**:165, 1911.
104. Kojima, B. M.: J. Physiol. **50**:45, 1916.
105. Johns, W. S.; O'Mulvenny, T. O.; Potts, E. B., and Laughton, N. B.: Am. J. Physiol. **8**:100, 1927.
106. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Arch. Surg. **18**:1708, 1929.
107. Baumann, E. J., and Marine, D.: Proc. Soc. Exper. Biol. & Med. **29**:1220, 1932.
108. Houssay, B. A., and Potick, D.: Compt. rend. Soc. de biol. **101**:940, 1929. Houssay, B. A., and Biasotti, A.: ibid. **104**:407, 1930; **105**:121 and 124, 1930.

resulted in a renewed and greatly increased interest in the hypophysioinsular relationship. A number of investigators took up the study of pancreotropic anterior pituitary extracts. Evans, Meyer, Simpson and Reichert [109] produced typical diabetic symptoms in dogs by continued treatment with an extract containing the growth-promoting substance; moreover, they were the first to establish diabetes that persisted after the treatment had been discontinued. The results of later workers depended largely on the species used in their experiments. Rats, mice and guinea pigs are almost insensitive to anterior pituitary extracts (Young [110]) and have at most temporary, mild symptoms. The histologic changes in the islets of rats are of hyperplastic nature.[111] The insulin content of the pancreas is correspondingly increased (Marks and Young [111d]). At the other extreme is the dog, which responds to daily injections of anterior pituitary extracts with typical symptoms of diabetes. With small doses the symptoms are transient, and the pancreas suffers no permanent damage; however, with large and especially with increasing doses permanent diabetes is produced with severe and irreversible damage to the islets. Correspondingly, the insulin content of the pancreas is much decreased (Best, Campbell and Haist [112]; Campbell and Best [113]; Campbell, Keenan and Best [114]; Marks and Young [111d]). The simultaneous administration of insulin with anterior pituitary extracts prevents damage to the islets (Campbell, Haist, Ham and Best [115]).

An intermediate position is occupied by the cat; this species responds much less well than the dog, but after partial resection of the pancreas permanent diabetes can be produced readily with anterior pituitary extracts (Lukens and Dohan [116]). Another specific feature of the cat is that both the clinical and the histologic picture can be reversed by insulin or dietary management in the early stages of the disease.

A certain percentage of experimental animals, both dogs and cats, are refractory.

The histologic observations in diabetes induced with anterior pituitary extracts are practically the same in dogs [117] and in cats.[116]

In refractory animals and in animals made diabetic only temporarily the changes are degranulation and hydropic swelling of the beta cells and vacuolation of the lining of small ducts. There is no clearcut correlation between the clinical course and the severity of the histologic damage. In permanent diabetes these changes are usually accentuated; in addition, a more or less extensive loss of cells, atrophy and hyalinosis of the islets are common though not constant find-

109. Evans, H. M.; Meyer, K.; Simpson, M. E., and Reichert, F. L.: Proc. Soc. Exper. Biol. & Med. **29**:857, 1932.

110. Young, F. G.: Biochem. J. **32**:513, 1938.

111. (*a*) Anselmino, K. J.; Herold, L., and Hoffman, F.: Klin. Wchnschr. **12**:1245, 1933. (*b*) Bierring, K.: Bull. d'histol. appliq. à la physiol. **11**:297, 1934. (*c*) Fichera, G.: Pathologica **30**:286, 1938. (*d*) Marks, H. P., and Young, F. G.: J. Soc. Chem. Industry **58**: 652, 1939. (*e*) Güthert, H.: Virchows Arch. f. path. Anat. **307**:175, 1940. (*f*) Richardson and Young.[9]

112. Best, C. H.; Campbell, J., and Haist, R. E.: J. Physiol. **97**:200, 1939.

113. Campbell, J., and Best, C. H.: Lancet **1**:1444, 1938.

114. Campbell, J.; Keenan, H. C., and Best, C. H.: Am. J. Physiol. **126**:455, 1939.

115. Campbell J.; Haist, R. E.; Ham, A. W., and Best, C. H.: Am. J. Physiol. **129**:328, 1940.

116. Lukens, F. D. W., and Dohan, F. C.: Science **92**:222, 1940; Endocrinology **30**:175, 1942.

117. Richardson, K. C., and Young, F. G.: Lancet **1**:1098, 1938. Ham, A. W., and Haist, R. E.: Nature, London **144**:835, 1939; footnote 39. Young, F. G.: New England J. Med. **221**:635, 1939. Dohan, F. C., and Lukens, F. D.: Am. J. Physiol. **125**:188, 1939. Dohan, F. C.; Fish, C. A., and Lukens, F. D.: Endocrinology **28**:341, 1941. Best, C. H.; Campbell, J.; Haist, R. E., and Ham, A. W.: J. Physiol. **101**:17, 1942. Campbell and Best.[113] Campbell, Keenan and Best.[114] Campbell, Haist, Ham and Best.[115] Richardson.[44]

ings. The alpha cells, as a rule, escape injury. In 2 dogs of Ham and Haist [39] the alpha cells were also involved; these animals were the only ones in the series to show fatty changes of the liver.

The mechanism of the action of anterior pituitary extract is by no means clearly understood; it probably involves several independent factors. The various extremely interesting physiologic, metabolic and biochemical aspects of the problem are covered in the papers already cited and in a number of others.[118]

The effects of hypophysectomy on the islets have been studied by Krichesky,[119] Adams and Ward, [120] Bakay [121] and Miller.[46]

Islet Cell Tumors and Insular Hyperglycemia.—Not all types of hyperglycemia are due to pancreatic disease. For the clinical aspects of the problem and discussions of extrapancreatic causes of hyperglycemia the reader is referred to articles published elsewhere.[122]

In the cases in which the pancreatic origin of hypoglycemic seizures was suspected and the pancreas explored, the findings were either obviously normal [123] or such as to fall easily within the extremely wide limits of normal variation, in spite of the authors' emphasis on the increased number and size of the islets.[124] In the case of Graham and Hartmann [93] even the cellular composition of the islets was normal. In a few cases the hyperplasia was close to what may be called adenomatous.[125] Grott [126] described a clinical picture of chronic pancreatitis combined with mild hyperinsulinism. Apart from these exceptional instances the pancreatic basis of hyperglycemia is, in the overwhelming majority of cases, a tumor of insular origin. This is the main reason why islet cell tumors and hypoglycemia have been put under one heading despite the fact that only about 20 per cent of all insular tumors are functional.

The pathology of the islet cell tumors is covered by the excellent review of Duff and Murray; [127] in the present paper only some of the most important points will be brought out.

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118. Hoffmann, F., and Anselmino, K. J.: Klin. Wchnschr. **12**:1436, 1933. Evans, E. I.: Proc. Soc. Exper. Biol. & Med. **30**:1370, 1933. Lucke, H.: Ergebn. d. inn. Med. u. Kinderh. **46**:94, 1934. Cope, O., and Marks, H. P.: J. Physiol. **83**:157, 1935. Houssay, B. A., and Foglia, V. G.: Compt. rend. Soc. de biol. **123**:824, 1936. Houssay, B. A.: Am. J. M. Sc. **193**:581, 1937. Long, C. N. H., in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 194. Lucke, H., and Koch, A.: Ztschr. f. d. ges. exper. Med. **103**:270 and 274, 1938. Marks, H. P., and Young, F. G.: J. Endocrinol. **1**:470, 1939; Lancet **1**:493, 1940. Campbell, J., and Keenan, H. C.: Am. J. Physiol. **131**:27, 1940. Young, F. G.: J. Physiol. **87**:13, 1936; Biochem. J. **32**:524, 1938; Endocrinology **26**:345, 1940.

119. Krichesky, B.: Proc. Soc. Exper. Biol. & Med. **34**:126, 1936.

120. Adams, A. E., and Ward, E. N.: Endocrinology **20**:496, 1936.

121. von Bakay, L., Jr.: Arch. f. d. ges. Physiol. **243**:733, 1940.

122. Harris, S.: Internat. Clin. **1**:9, 1932; J. A. M. A. **101**:1958, 1933. Wauchope, G. M.: Quart. J. Med. **26**:117, 1933; Practitioner **147**:498, 1941. Womack, N. A.: Surgery **2**:793, 1937. Nicholson, W. M., and Hart, D.: Internat. Clin. **2**:251, 1938. Wilder, R. M.: Clinical Diabetes and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940. Conn, J. W.: J. A. M. A. **115**:1669, 1940. Chaves, N.: Neurobiologia **3**:147, 1940. Hart, J. F., and Lisa, J. R.: Internat. Clin. **4**:97, 1941.

123. Allan, F. N.: Arch. Int. Med. **44**:65, 1929. Finney, J. M. T., and Finney, J. M. T., Jr.: Ann. Surg. **88**:584, 1928. Thomason, G.: West. J. Surg. **43**:185, 1935. Graham and Hartmann.[93]

124. Phillips, A. W.: J. A. M. A. **96**:1195, 1931. Magner, W.: Canad. M. A. J. **45**:49, 1941. Valk, A. de T., and MacMillan, E. A.: North Carolina M. J. **2**:648, 1941.

125. Lang, F. J.: Virchows Arch. f. path. Anat. **257**:235, 1925. Dannenberg, A. M.; Bell, M. A., and Gouley, B.: J. Pediat. **7**:44, 1935. McCaughan, J. M., and Broun, G. C.: Ann. Surg. **105**:354, 1937.

126. Grott, J. W.: Gastroenterologia **66**:72, 1941.

127. Duff, G. L., and Murray, E. G. D.: Am. J. M. Sc. **203**:437, 1942.

The microscopic diagnosis of the insular origin of a pancreatic tumor depends (1) on the structure of the growth and (2) on the staining reactions of the cells. The structural criteria as given by Duff and Murray are these: short anastomosing cords, one to three cells thick, separated by capillaries, with which the cells are in intimate connection. The similarity to normal islets is striking in some cases, less so in others. The staining reactions are of great importance. Normal islet cells are stained supravitally by neutral red (Bensley[1]), and this property is shared by a variable proportion of islet tumor cells. The staining reaction may persist even in tissue cultures.[128] The neutral red stain, by the way, does not permit differentiation between cell types; it merely indicates insular origin.

The overwhelming majority of islet cell tumors may be classified as noncancerous adenoma; some, however, are frank carcinoma, and there is an intermediate group, showing some local invasion but no tendency to form metastases.

The tumors classified as adenoma are of three types, according to Isaji:[129] solid, trabecular and tubular. The trabecular type is the most common. Most of the tumors diagnosed as adenoma display a strong tendency toward hyaline thickening of their stroma. The tumors classified as carcinoma may be of a solid type or of a type imitative of small ducts and acini.

Unfortunately, the great majority of reported islet tumors were examined only with routine stains, which permit no differentiation between cell types. Only thirty papers were found in which the use of some kind of specific stain for the identification of cell types was reported. In 10 cases the stains were unsuccessful, demonstrated no specific granules or gave results that were not clearcut enough to permit conclusions.[130] In 8 cases cells were found that resembled more or less, but were not quite like, normal beta cells.[131] In 10 cases typical beta cells were found.[132] Cells more or less closely resembling the alpha type were observed in cases of functional adenoma [133] and in a case of nonfunctional adenoma of Warren [29]

128. Murray, M. R., and Bradley, C. F.: Am. J. Cancer **25**:98, 1935.

129. Isaji, M.: Frankfurt. Ztschr. f. Path. **53**:178, 1938.

130. (*a*) Smith, M. G., and Seibel, M. G.: Am. J. Path. **7**:723, 1931. (*b*) Derick, C. L.; Newton, F. C.; Schulz, R. Z.; Bowie, M. A., and Pokorny, N. A.: New England J. Med. **208**: 293, 1933. (*c*) Ross, D. I., and Tomasch, J. M.: Arch. Surg. **28**:223, 1934. (*d*) Rienhoff, W. F., and Lewis, D.: Bull. Johns Hopkins Hosp. **54**:386, 1934. (*e*) Ziskind, E.; Bayley, E., and Mauer, E. F.: Arch. Int. Med. **60**:753, 1937. (*f*) Kusunoki, T., and Munakata, M.: Arch. f. klin. Chir. **188**:272, 1937. (*g*) Joachim, H., and Banowitch, M. M.: Ann. Int. Med. **11**:1754, 1938. (*h*) Bailey, O. T., and Cutler, E. C.: J. internat. de chir. **3**:303, 1938. (*i*) Bergonzi, M.: Riv. sper. di freniat. **63**:161, 1939. (*j*) Meyer, K. A.; Amtman, L., and Perlman, L.: J. A. M. A. **117**:16, 1941. (*k*) Gomori.[15]

131. (*a*) Bast, T. H.; Schmidt, E. R., and Sevringhaus, E. L.: Acta chir. Scandinav. **71**:82, 1932. (*b*) Graham, E. A., and Womack, N. A.: Surg., Gynec. & Obst. **56**:728, 1933. (*c*) Whipple, A. O., and Frantz, V. K.: Ann. Surg. **101**:1299, 1935. (*d*) Friedman, N. B.: Arch. Path. **27**:994, 1939. (*e*) Bargmann, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **29**:562, 1939. (*f*) Beck, J. E., and Segrest, G. O.: J. M. A. Alabama **9**:40, 1939. (*g*) Burtness, H. I.; Koehler, A. E., and Saint, J. H.: Ann. Int. Med. **14**:1915, 1941. (*h*) Winters, W. L.; Gottards, P., and McNealy, R. W.: West. J. Surg. **49**:488, 1941.

132. (*a*) Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: J. A. M. A. **93**:674, 1929. (*b*) Womack, N. A.; Gnagi, W. B., and Graham, E. A.: ibid. **97**:831, 1931. (*c*) Carr, A. D.; Parker, R.; Grove, E.; Fisher, A. O., and Larimore, J. W.: ibid. **96**:1363, 1931. (*d*) O'Leary, J. L., and Womack, N.: Arch. Path. **17**:291, 1934. (*e*) Fraser, R.; Maclay, W. S., and Mann, S. A.: Quart. J. Med. **31**:115, 1938. (*f*) Campbell, W. R.; Graham, R. R., and Robinson, W. L.: Am. J. M. Sc. **198**:445, 1939. (*g*) Gray, L. M.: Am. J. Path. **18**:633, 1942. (*h*) Kerwin, A. J.: Am. J. M. Sc. **203**:363, 1942. (*i*) Smith and Seibel.[130a] (*j*) Laidlaw.[38]

133. Wolf, A.; Hare, C. C., and Riggs, H. W.: Bull. Neurol. Inst. New York **3**:232, 1933. Laidlaw.[38] Smith and Seibel.[130a] Derick and others.[130b] Graham and Womack.[131b] Whipple and Frantz.[131c] Burtness and others.[131g] Howland and others.[132a] Fraser and others.[132e] Campbell and others.[132f] Kerwin.[132h]

(erroneously identified with the beta type). In 2 cases reported by Howland and co-workers [132a] and by Campbell and co-workers [132f] respectively, the majority of the cells contained alpha granules. There are three reports on cells containing both alpha and beta granules (Howland and associates [132a]; Smith and Seibel [130a]; Kerwin [132h]). D cells were found by Bargmann [131e] only. There seems to be no correlation between the insulin content as determined by bioassay [134] and the cytologic character of the tumor.

Since the specific stains used in most of the cases mentioned were of the neutral gentian type, the results should be evaluated with some caution. It would be worth while to reexamine as many as possible with more reliable methods.

Apart from Warren's [29] case with cells resembling the alpha type, there are no data on the cytologic nature of the tumors grouped as nonfunctional adenoma. With routine stains they are indistinguishable from the ones segregated as functional adenoma.

Islet tumors in animals were reported by Bru,[135] Slye and Wells [136] and Hueper.[137]

COMMENT

According to all experimental and pathologic evidence, the beta cells are concerned in some important way with the regulation of carbohydrate metabolism. However, it is by no means proved that they actually secrete insulin or that the beta granules are the morphologic expression of insulin content. In fact, insulin precipitated from commercial solutions by histologic fixatives does not show the staining properties of beta granules [45]; furthermore, tumors with no demonstrable beta cells were found to have high insulin activity. Therefore, the part played by the beta cells in carbohydrate metabolism is poorly understood. The function of the alpha cells is entirely in the dark. The finding by Ham and Haist [39] of alpha cell degeneration associated with fatty liver may be a hint at their possible role as producers of lipocaic (Dragstedt [138]).

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134. Howland and co-workers.[132a] Derick and co-workers.[130b] Bailey and Cutler.[130h] Campbell and co-workers.[132f]

135. Bru, P.: Rev. méd.-chir. d. mal. du foie **2**:40, 1927.

136. Slye, M., and Wells, H. G.: Arch. Path. **19**:537, 1935.

137. Hueper, W. C.: Arch. Path. **22**:220, 1936.

138. Dragstedt, L. R.: Ann. Surg., to be published.

Notes and News

Appointments.—Roscoe R. Spencer, medical director, United States Public Health Service and assistant chief of the National Cancer Institute, Bethesda, Md., has been appointed chief of the institute, succeeding Carl Voegtlin, retired.

Oswald Avery, member of the Rockefeller Institute for Medical Research, has been made emeritus, having reached the retirement age.

C. P. Rhoads, director of Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, has been given leave of absence to become chief of the Medical Division of the Chemical Warfare Service of the United States Army, with the rank of colonel. F. W. Stewart, pathologist, has been appointed acting director, with Howard Taylor Jr. as his assistant.

At Yale University Harry S. N. Greene, associate professor of pathology and surgery, has been appointed professor of pathology.

Burrell O. Raulston, professor of medicine, has been appointed professor of bacteriology and dean of the school of medicine of the University of Southern California at Los Angeles. He succeeds Seeley G. Mudd, who will continue as professor of experimental medicine.

Deaths.—Leslie T. Webster, member of the Rockefeller Institute for Medical Research, known for his work on experimental epidemiology, encephalitis and rabies, died July 12, 49 years old.

Carl W. Apfelbach, professor of pathology in the University of Illinois College of Medicine, pathologist and medical director of the Presbyterian Hospital, Chicago, died June 25, 49 years old.

Arthur T. Henrici, professor of bacteriology and immunology in the University of Minnesota, died April 23, 1943, aged 54 years.

Karl Landsteiner died on June 25 (see page 234).

Need for Pathologic Material.—In view of the need for pathologic material in undergraduate and graduate education, the committee on pathology of the National Research Council urges that all who have suitable anatomic specimens forward them to the curator of the Army Medical Museum, Washington, D. C., for correlation and distribution to other central agencies and to teaching institutions. Material from the following is particularly wanted: the malarial diseases, bacillary dysentery, endamebiasis, the schistosomiases, filariasis, the trypanosomiases, relapsing fever, the leishmaniases, the rickettsial diseases, yellow fever, cholera, plague and yaws. On application to the curator, arrangements for transportation will be made.

Institute for Forensic Medicine.—Announcement has been made that plans are under way to establish a complete central institute for forensic medicine in New York city.

Obituaries

KARL LANDSTEINER, M.D.

1868–1943

On June 25, 1943, shortly after passing the seventy-fifth birthday of a life devoted to pioneering research, Dr. Karl Landsteiner died from "a heart attack" which overtook him at work in his laboratory at the Rockefeller Institute. Author of "The Specificity of Serological Reactions" and about three hundred and thirty articles reporting results of significant research, Dr. Landsteiner was the founder of several branches of immunology.

Dr. Landsteiner is best known for his discovery, in 1900-1901, of the division of human beings into blood groups by isoagglutination, which made blood transfusion the safe procedure it is today, and therefore is responsible for the saving of many thousands of lives. He also discovered the agglutinogens M and N which together with the blood groups are applied in forensic medicine for the identification of blood stains and in disputed parentage. He developed methods of coupling simple chemical compounds to proteins, thereby producing antigens whose specificity depended mainly on the groupings thus introduced into the protein molecule. Extending this technic to a host of chemical compounds, he demonstrated the correlation between the specificity of serologic reactions and the chemical structure of the antigen. The field of immunochemistry which he founded in this manner has proved indispensable in the solution of many problems in bacteriology and immunity. He introduced dark field illumination for demonstrating spirochetes and showed that alcoholic extracts of normal tissue contain the principle responsible for Wassermann's complement fixation (an observation on which is based the current use of beef heart lipids as antigen in the test). He elucidated the immunologic mechanism of paroxysmal hemoglobinuria. By successfully transmitting the virus of poliomyelitis to monkeys he inaugurated the experimental study of this disease. In studies on drug allergy and contact dermatitis he developed technics of inducing sensitivity to simple chemical compounds in animals. In these experiments he adduced considerable evidence to show that this depends on an antigen-antibody reaction and that the simple chemicals responsible for the disease acquire their antigenic properties by combining with body proteins. He demonstrated the presence in human blood cells of an agglutinogen Rh, which has proved to be of considerable importance in clinical medicine.

For his contributions to medical knowledge, many honors, including the Nobel Prize in Medicine in 1930, were accorded to Dr. Landsteiner. In a citation read in his honor at the University of Chicago he was called "the world's greatest authority on the mechanism of immunity," and a Harvard citation stated "he founded a school of thought which has penetrated wherever immunologists are at work."

A. S. WIENER.

KARL LANDSTEINER, M.D.
1868-1943

Books Received

AIR-BORNE INFECTION: SOME OBSERVATIONS ON ITS DECLINE. Dwight O'Hara, M.D., professor of preventive medicine, Tufts College Medical School; visiting physician, Boston City Hospital; physician in chief, Waltham Hospital. Pp. 114. Price $1.50. New York: The Commonwealth Fund, 1943.

These discussions of the falling incidence of air-borne infections are interesting. The effects on the reduction of modern preventive and sanitary measures, of improved living conditions and of spontaneous and artificial immunizations are analyzed. It is pointed out that the starting of the reduction in some cases before control measures were under way remains unexplained. The recent advances in knowledge of scarlet fever are largely ignored. The statement (page 63) "We now know that one and the same organism can cause a septic sore throat, scarlet fever, and erysipelas, not only in different individuals but at the same time in one person," is open to question.

A SYNOPSIS OF CLINICAL SYPHILIS. James Kirby Howles, B.S., M.D., M.M.S., professor and director of the department of dermatology and syphilology of the Louisiana State University School of Medicine; senior visiting physician, Charity Hospital of Louisiana at New Orleans; visiting physician, French Hospital, Mercy Hospital, Hotel Dieu, Southern Baptist Hospital and Touro Infirmary. Pp. 671, with 121 illustrations in the text and 2 color plates. Price $6. St. Louis: C. V. Mosby Company, 1943.

There are three sections: (1) syphilis in general—the process, the stages, the diagnosis, the treatment of acquired syphilis, the prognosis; (2) systemic and regional syphilis—acquired syphilis of the mucous membranes, the cutaneous appendages, the eye and the ear, the respiratory system, the cardiovascular system, the gastrointestinal tract, the liver and biliary tract, the pancreas, the spleen, the skeletal system, the central nervous system, the endocrine glands; (3) familial and public health aspects—the epidemiology of syphilis, syphilis and pregnancy, congenital syphilis, the organization and social service aspects of the syphilis clinic. At the end are a historical note, a select bibliography and a good index. The illustrations show mostly gross external lesions. This compact octavo volume gives a clear, well arranged instructive synopsis of clinical syphilis with stress on treatment and prevention.

THE INTERNATIONAL CANCER RESEARCH FOUNDATION. A Report of Activities During 1942. Pp. 120. Philadelphia: International Cancer Research Foundation, 1943.

REHABILITATION OF THE WAR INJURED: A SYMPOSIUM. Edited by William Brown Doherty, M.D., and Dagobert D. Runes, Ph.D. Pp. 684. Price $10. New York: Philosophical Library, Inc., 1943.